

THE PUPIL AND ACCOMMODATION:
OBSERVATIONS ON THEIR NERVOUS CONTROL
IN HEALTH AND DISEASE

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by

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CHAPTER I

INTRODUCTION

The subject of this thesis is the nervous control of the syphilitic and Holmes-Adie pupils, and the disturbance of accommodation in the Holmes-Adie syndrome. The innervation of the iris and ciliary muscle in the normal is also studied.

The work was carried out at the Neurological Unit, the Northern General Hospital, Edinburgh (1953-1955), with the encouragement of Dr. John Marshall; and at the Neurological Research Unit, the National Hospital, Queen Square (1956-1957), under the guidance of Dr. E.A. Carmichael.

Much attention has been paid to the mechanism of pupillary abnormalities since the description of miotic pupils in association with spinal disease by Argyll Robertson in 1869, and the observations by Holmes (1931) and Adie (1932) on the tonic pupil. But there remain many unsolved problems of which the following are the most important:-

1. What is the mechanism of miosis in the syphilitic pupil?
2. Is there a separation of the pathways for the reaction of the pupil to light and to convergence? If there is, where are the fibres conveying the light-reflex damaged in syphilis?
3. What causes the tonic reaction of the pupil in the Holmes-Adie syndrome, and where is the lesion situated in this disorder?

In this thesis, solutions to questions 1 and 3 are sought.

Likewise, since Helmholtz's brilliant analysis of accommodation (1909), opinion has been sharply divided whether or not there is a sympathetic innervation of the ciliary muscle. It was thought necessary to solve this question before turning to the study of abnormal accommodation in the Holmes-Adie syndrome.

The general approach of the investigation was to ascertain the role played by each component of the autonomic nervous system - sympathetic and parasympathetic - in the causation of disturbances of the pupil and accommodation. This was done by stimulating or temporarily paralyzing each component in turn: procaine blocks of the cervical sympathetic chain and drugs instilled in the conjunctival sac were the chief methods used. Pupil size was usually estimated by simple clinical means, but on one occasion precise pupillography was employed. Accommodation was accurately measured with a coincidence optometer.

The most interesting findings were that interruption of the sympathetic did not influence normal accommodation, nor did it essentially alter the tonic pupil in the Holmes-Adie syndrome. In this disorder it was shown that different parasympathomimetic drugs had an increased action on both the sphincter pupillae and the ciliary muscle.

The main conclusions reached in this thesis are that there is no sympathetic control of normal accommodation, and that the sympathetic innervation plays no fundamental part in the pupillary abnormalities of syphilis and the Holmes-Adie syndrome. In addition, it is likely that the tonic reaction affecting the pupil and accommodation depends largely on hypersensitivity of the

sphincter pupillae and ciliary muscle to acetylcholine.

It is hoped that the evidence provided will settle the controversial question of the nervous control of accommodation in man, and will give a lead to future research into the derangements of the pupil and of accommodation.

CHAPTER II

THE LITERATURE

In this chapter will be discussed the general literature relevant to the theories of the pathogenesis of the syphilitic pupil and the Holmes-Adie syndrome. The more detailed literature dealing with the complete denervation of the iris, the mode of action of locally instilled cocaine, and the innervation of the ciliary muscle will be reviewed later, in each appropriate section of the thesis.

THE PUPIL IN SYPHILIS

In the Edinburgh Medical Journal of 1869, Douglas Argyll Robertson described a series of pupillary abnormalities associated with spinal disease. In four patients the signs were extreme miosis, inequality, and insensibility to light with preservation of the contraction to accommodation for near vision. In order to examine the optic fundi, he instilled atropine into his first patient's eyes and noted an only partial dilatation of the pupils. He thought that the irides were normal in appearance, and he did not describe any irregularity of the pupil margin. He mentioned the occurrence of ptosis in one case.

The term "Argyll Robertson syndrome" has since been applied to different abnormalities of the pupils. It may be used to denote a loss of the light reflex with retention of the reaction to near vision (Wilson, 1921; Duke-Elder, 1949), or it may be restricted to the pupil that is miotic in addition to showing the isolated

reflex paralysis to light (Langworthy and Ortega, 1943).

Irregularity of the pupil outline and atrophy of the iris may or may not be included in the definition, and very seldom is the reaction to atropine tested.

Argyll Robertson did not know the cause of the abnormal pupils he described. It has since been shown that they are often, but not invariably, due to syphilis. Syphilis may be evoked as the aetiological factor with greater confidence when miosis is present in addition to the isolated reflex paralysis to light, a fact which has been emphasized by Behr (1925), Duke-Elder (1949), Naquin (1954), Apter (1954), Rouques (1954), and Lassierra and Sanchez-Arroyo (1955).

The Mechanism of the Disturbances in the Syphilitic Pupil

Investigators interested in analysing the disturbances in the syphilitic pupil have had to reconcile an interruption of the light reflex with the occurrence of miosis; they have usually sought to account for the two phenomena by a single lesion. The theories advanced will be discussed under three headings:-

- i. The isolated reflex paralysis to light.
- ii. The miosis.
- iii. The site of the lesion.

i. The Isolated Reflex Paralysis to Light

Three main theories have been proposed to explain the dissociation of the two pupillary reflexes. First, and more commonly, it has been assumed that there are two separate pathways for these two reflexes. Merritt and Moore (1933) and Harris (1935) claimed that this separation occurred in the mid-brain, whereas Nathan and Turner

(1942) produced evidence for a divergence of the pathways in the ciliary ganglion; the near-reflex fibres synapse in the episcleral ganglia. Second, it has been emphasized that the response to accommodation-convergence is more powerful than the reaction to light, and therefore more likely to remain intact (Langworthy and Ortega, 1943; Benton, 1953). Third, Apter (1954) has suggested that the pupillary reaction to near vision is not neurogenically determined, but it is wholly dependent on mechanical factors - the result of accommodation itself. She supposes that the forward movement of the ciliary muscle during accommodation is sufficient to cause a centripetal relaxation of the iris as a whole, with resulting pupillary constriction. In her opinion, abolition of the light reflex is due to atrophy of the iris resulting from obliteration of the iridal spiral blood-vessels.

11. The Miosis

Equally varied explanations have been put forward for the miosis.

The three most important theories are as follows:-

1. Interruption of the sympathetic innervation.
2. Irritation of the parasympathetic nerves.
3. Structural changes in the iris itself.

Argyll Robertson was the first to postulate that the sympathetic innervation of the pupil is destroyed, with resulting weakness of the dilator pupillae and constriction of the pupil. He wondered if this would account for the failure of atropine to dilate the pupil, and suggested that in addition to paralysing the sphincter pupillae atropine acts by stimulating the dilator. He believed the paralysis of the dilator pupillae to be due to an interruption of

nerve fibres arising from the cilio-spinal centre - "true spinal nerves, though associated with sympathetic filaments".

To explain the miosis and the failure of atropine to dilate the pupil, a sympathetic lesion was also proposed by later authors (Grainger-Stewart, 1879; Marina, 1901; Dupuy-Dutemps, 1905; Wilson, 1921; Lhermitte and De Massary, 1935; Leathart, 1941; Thiebaut and Helle, 1953). Merritt and Moore (1933) assumed that the sympathetic fibres are destroyed in the mid-brain, whereas Langworthy and Ortega (1943) thought that they are involved by a neuritis at the nerve terminals in the iris. Uriarte (1935) went further and suggested that the abolition of the light reflex, as well as the miosis, could be explained by interference with the sympathetic innervation - a view convincingly rejected by Spiegel and Scala (1940). Syphilitic pupils are often associated with ptosis, which has also been ascribed to a sympathetic lesion by Dupuy-Dutemps (1905), Langworthy and Ortega (1943), Brain (1951) and Naquin (1954).

The theory of overaction of the parasympathetic causing a miosis was considered and discarded by Argyll Robertson because of the inability of atropine to overcome fully the pupillary constriction. It was accepted by Behr (1925) and Ingvar (1928); recently it was revived by Lowenstein (1956) who, contrary to accepted opinion, thought that atropine has an exaggerated effect in dilating the constricted syphilitic pupil.

Last must be mentioned the opinion held by Apter (1954), that it is the atrophy of the iris which is responsible for the small pupil and, incidentally, for the loss of the light reflex. The atrophic changes in the syphilitic pupil were described in detail by

Dupuy-Dutemps (1905) and McGrath (1932). McGrath, and Langworthy and Ortega (1943) pointed out that the light rigidity varies with the extent of the atrophy, and first affects those segments of the iris where the atrophy begins.

iii. The Site of the Lesion

The location of the lesion responsible for the syphilitic pupil is still unknown - indeed direct pathological investigations have been inconclusive. The following sites have been proposed:-

1. The cilio-spinal centre in the spinal cord
(Argyll Robertson, 1869).
2. The afferent fibres of the light reflex arc:-
 - a. Optic tract and surface of diencephalon (Ingvar, 1928).
 - b. Superior brachium quadrigeminum (Leathart, 1941).
3. The mid-brain reflex centres:-
 - a. Afferent fibres before synapsing (Wilson, 1921; Behr, 1925; Wilkinson, 1927; Merritt and Moore, 1933; Harris, 1935; Lowenstein, 1956).
 - b. Synapses in the Edinger-Westphal nucleus (Spiegel and Scala, 1936).
 - c. Cells of Edinger-Westphal nucleus (Levinsohn, 1917).
4. Oculomotor nerve (Bauer, 1918).
5. Ciliary ganglion (Marina, 1901; Dupuy-Dutemps, 1905; McGrath, 1932).
6. Peripheral nerve endings (Orlando and Gambino, 1940; Langworthy and Ortega, 1943; Apter, 1954).

Certainly, before the problems of the syphilitic pupil can be solved, more information will be needed as to the nature of its more

fundamental defects - the miosis and the isolated reflex paralysis to light. The present work is confined to investigating the possible role of a sympathetic lesion in causing the miosis and the ptosis which is often associated with the syphilitic pupil.

THE HOLMES-ADIE SYNDROME

In 1936, Bramwell suggested that the eponymous title "Holmes-Adie syndrome" be given to the clinical complex of a slowly reacting pupil and absent tendon reflexes, in recognition of the descriptions by Holmes (1931) and Adie (1932). Both authors had emphasized the chief clinical features - dilatation of the pupil, apparent loss of the reaction to light, slow constriction and relaxation in response to near and distant vision, impaired or delayed accommodation and partial loss of tendon reflexes. In addition, they mentioned the occasional slow dilatation of the pupil in a dark room, and its constriction when the patient weeps.

Credit must go to Adie in particular for stressing the benign nature of the disorder and distinguishing it clearly from neurosyphilis, but the syndrome had been recognised wholly or in part many years previously. In Germany, Strasburger, Saenger and Nonne independantly described the clinical manifestations in 1902. In this country, Markus (1906) reported in detail a slowly reacting pupil in a patient who also had a delay in accommodation and a loss of tendon reflexes. The first account in the French literature was given by Weill and Reys (1926). It is probable in fact that the first case was published in 1818 by James Ware, an English surgeon (See Riddell, 1937).

The Holmes-Adie pupil has also a definite evolution -- there is frequently an early stage of internal ophthalmoplegia when the pupil is fixed to both light and convergence, and accommodation is paralysed. After an interval of weeks or months there follows the second stage of a slow response to convergence and to light, and an apparent recovery of accommodation. (Rothmann, 1903; Azenfeld, 1919; Reitsch, 1925; Alajouanine and Morax, 1938; Van Leeuwen, 1946; Stürup, 1946; Kyrieleis, 1951). Adie recognised the stage of internal ophthalmoplegia; he referred to it and other variants of the benign disorder which he described by the term "incomplete form".

Other workers have drawn attention to the variability of the pupillary anomalies: so much so that Schaeffer (1937), Alajouanine and Morax (1938), and Lowenstein and Friedman (1942) stated that atypical Holmes-Adie pupils may appear to be identical with the abnormal pupils caused by syphilis. Even if one disagrees with this extreme view, it is true that some of the features said to distinguish the Holmes-Adie from the syphilitic pupil are not valid. For instance, it has become more frequently recognised that bilaterally abnormal pupils with irregular margins are relatively common in the Holmes-Adie syndrome. (Van Leeuwen, 1946; Ruttner, 1947). Graveson (1949) reported irregularity of all the pupils he observed, and bilateral changes in seven out of fifteen patients; Kyrieleis (1951), who examined sixty patients with the Holmes-Adie syndrome, found both pupils involved in one third of them. In view of the alleged importance of miosis as a characteristic feature of the syphilitic pupil, its occurrence in the Holmes-Adie syndrome may give rise to diagnostic difficulties.

In five of his fifteen patients Graveson (1949) found a pupil of 3 mm. or less in diameter, and miotic pupils were also described by James (1944), Sykowski (1951), and Voisin and Juge (1956). Even atrophy of the iris has been reported in the Holmes-Adie syndrome (Wagner, 1938; Alajouanine and Morax, 1938; Van Leeuwen, 1946).

Definition of the Tonic Pupillary Reaction

In spite of the variability of the clinical features, the typical Holmes-Adie pupil can be identified by its tonic reaction. By this term is generally meant the slowness of pupillary constriction and the even slower pupillary dilatation in response to near and far vision respectively. But it has also been noted that the reaction to convergence may be remarkably wide in its range, considering that it often follows a stage of complete paralysis (Strasburger, 1902). Not only is the reaction to convergence well preserved when compared to the reaction to light, but it may in fact be excessive. For instance, the abnormal pupil which is initially larger than its normal fellow may become the smaller of the two pupils after convergence - a feature emphasized by Alajouanine and Morax (1938) and Heersema and Moersch (1939).

It will be shown later in this thesis that different pupils in the Holmes-Adie syndrome vary in the degree to which they show the tonic reaction, and that the same pupil may exhibit similar variations during the course of the disorder. In assessing the degree of tonicity, two criteria will be used in this work - slowness of pupillary movement and preservation in the range of movement.

The Actiology of the Holmes-Adie Syndrome

The actiology of the Holmes-Adie syndrome is unknown. This disorder has been found with many diseases, including encephalitis (Gayer-Morgan and Symonds, 1927), disseminated sclerosis and diabetes mellitus (Holmes, 1931), pernicious anaemia (Petit and Delmond, 1936), Raynaud's disease (Heersema and Moersch, 1939), diphtheria (Marx, 1952; Bonamour, 1952), narcolepsy (De Morsier and Franceschetti, 1953), amyotrophic lateral sclerosis (Sproffkin, 1953) and status dysraphicus (Manghi and Saginario, 1954). The multiplicity of widely differing causes suggests that these are chance associations. Emotional disorders and frank mental illness have also been evoked as causal factors in the Holmes-Adie syndrome (Petit and Delmond, 1936; Heuberger, 1954). Again, the incidence of these psychological disturbances is probably no greater in the Holmes-Adie syndrome than in a comparable population (Heersema and Moersch, 1939).

Even since Adie's rejection of syphilis as an actiological agent, there have been reports of tonic pupils where a diagnosis of syphilis was established by specific tests of the blood and cerebro-spinal fluid (Lhermitte, 1937; Alajouanine and Morax, 1938; Subirana and Oller-Daurella, 1947; Sproffkin, 1953). It may be that, in rare instances, syphilis is the cause of the syndrome. There is more evidence to substantiate a causal relationship between local abnormalities of the skull and orbit, and tonic pupils. Thus, there are a few well authenticated cases resulting from injuries to the orbit (Axenfeld, 1906; Ohm, 1907; Cords, 1930), alcohol injection of the ciliary ganglion (Weekers, 1948), tumours of the skull and orbit (Garcin and Kipfer, 1936) and Paget's disease of the skull

(Dynes, 1942). In the majority of cases, however, the aetiological factors are unknown.

The Site of the Lesion

The following sites have been suggested as being the location of the lesion causing the pupillary abnormalities of the Holmes-Adie syndrome:-

1. The diencephalon (Kennedy et al, 1938; Barré et al, 1950; Bonamour, 1952).
2. The supra-nuclear oculomotor fibres (Lowenstein and Friedman, 1942).
3. The pretectal region of the mid-brain (McKinney and Frocht, 1940).
4. The oculomotor nerve nucleus (Behr, 1921; Holmes, 1931; Adie, 1932; Kyrieleis, 1951).
5. The ciliary ganglion (Ohm, 1907; Magitot, 1911; Garcin and Kipfer, 1936; Adler and Scheie, 1940; Leathart, 1942; Weekers, 1948; Lenz, 1952; Rieger, 1953).
6. The iris muscle itself (Saenger, 1902).

As with the site of the lesion in the syphilitic pupil, this multiplicity of theories reveals our ignorance. There has been only one anatomic study (Bittner, 1947) which demonstrated degeneration of ganglion cells in the ciliary ganglion. Owing to the benign nature of the disorder, it is understandable that pathological material is difficult to obtain.

Without the benefit of adequate pathological examinations, we must depend on deductions made from clinical observations. Our attention may be confined to theories 4, 5 and 6, because only they

would account for the loss or impairment of the direct reaction to light and the preservation, in a unilateral case, of the consensual reaction on illuminating the abnormal eye. There is no evidence in support of a "myotonic iris" (theory 6); in fact, the tonic pupil has only seldom been reported in congenital myotonia (Hoche, See Gehroldt, 1906). Obviously, the theories of parasympathetic denervation of the iris (theories 4 and 5) do not account for all the features of the Holmes-Adie pupil. In particular, they fail to explain the distinctive tonic reaction, the occasional miosis and the isolated reflex paralysis to light. Many workers were aware of these difficulties and sought to fill the gaps in their theories by postulating additional mechanisms for the tonic reaction, the miosis and the isolated reflex paralysis to light.

The Tonic Reaction

Three main hypotheses have been advanced and they will be considered separately from the theories already listed because they deal specifically with the tonic reaction, as opposed to the location of the lesion:-

1. A Lesion of the Sympathetic Innervation

Alajouanine and Morax (1938) described an increased sensitivity of the Holmes-Adie pupil to sympathomimetic and parasympathomimetic drugs, and concluded that it was liberated from sympathetic as well as parasympathetic control. A lesion of the sympathetic was also thought likely by Weill and Reys (1926), Barré and Klein (1934), Barré et al (1950), and De Morsier and Franceschetti (1953). Other authors, however, assumed the sympathetic to be intact (Holmes, 1931; Scheie, 1940; McKinney and Frocht, 1940; Langworthy and Ortega, 1943).

Adie (1932) and Kennedy et al (1938) subscribed to the idea of a derangement of sympathetic function, but did not specify if they envisaged an increase or a decrease in its activity.

ii. An Overactivity of the Sympathetic Innervation

Garcin and Kipfer (1936), and Lowenstein and Friedman (1942) considered the sympathetic to be overactive.

iii. Altered Sensitivity of the Sphincter Pupillae

The concept of hypersensitivity of a denervated structure was put forward by Cannon and Rosenblueth (1949) whose work on the subject is comprehensive. Their law of denervation states that when a chain of neurons is severed, there results after an interval an hypersensitivity of the distal elements and effectors to the action of nerve impulses, and to certain chemical agents either injected parenterally or applied locally.

The hypothesis of increased sensitivity of the sphincter pupillae was first put forward by Adler and Scheie (1940). They showed that the tonic pupil constricts after the conjunctival instillation of the weak parasympathomimetic substance acetyl B methyl choline, in concentrations which have no effect on normal pupils. Scheie (1940) therefore concluded that there would be a similar sensitivity to acetyl choline released within the sphincter pupillae by any surviving parasympathetic nerve fibres; thus he accounted for the slow constriction during convergence of the eyes. He explained the slowness of relaxation as the delay required for the destruction of acetyl choline by cholinesterase. Graveson's deductions (1949) were similar to Scheie's, except that he regarded the sluggish constriction of the pupil simply as a sign of weakness

of the sphincter pupillae.

Small Pupils in the Holmes-Adie Syndrome

Graveson (1949) suggested that there is a sympathetic defect, in addition to a parasympathetic lesion, in those cases where the pupil is small. He also proposed the same explanation for the occasional ptosis associated with a tonic pupil, as described by Alajouanine and Morax (1938), and Moore (1931).

The Isolated Reflex Paralysis to Light in the Holmes-Adie Syndrome

Holmes (1931) ascribed the preservation of the reaction to convergence to the fact that it is a stronger stimulus than the reaction to light. The problem of the isolated reflex paralysis to light is the same in this disorder as in the syphilitic pupil, and has already been discussed on p. 5.

It seems that before speculating on the mechanism of the pupillary abnormalities in the Holmes-Adie syndrome, it would be more rewarding to investigate the distinctive property of these pupils - their tonic reaction. The three theories outlined above could be tested as follows:-

1. Is there any evidence of overaction of the sympathetic?
2. Conversely, is the sympathetic innervation damaged?
3. Does the tonic pupil react in an hypersensitive manner to various parasympathomimetic substances? Does this sensitivity account fully for all the abnormal features?

In this thesis, questions 1 and 2 are answered; question 3 raises further problems which remain unsolved.

Accommodation in the Holmes-Adie Syndrome

As well as the various abnormalities of the pupil, disturbances of accommodation have been found in the Holmes-Adie syndrome.

Kyrieleis (1951) stated that tonic accommodation occurs in more than 20% of cases, whereas Graveson (1949) found it in 16 out of 22 affected eyes.

There is general agreement that with the internal ophthalmoplegia which may be the early stage of the syndrome there is often a paralysis or weakness of accommodation. It has already been mentioned that the fixed pupil usually changes into a tonic one in the course of weeks or months; this second stage is accompanied by an improvement in accommodation (Holmes, 1931; Van Leeuwen, 1946). From the clinical standpoint, the early stage may be manifested by blurring of vision - the patient is unable to read small print with the affected eye owing to recession of the near point. During the later stage, the range of accommodation is restored with improvement of vision, but there often remains a slight disability - accommodation may be delayed before either the near or the distant object is seen clearly.

As in the case of the slow pupillary contraction, slow accommodation has been termed tonic. Graveson (1949) reported tonic accommodation for near vision in the majority of his patients. Other authors found that the greater delay in accommodation occurs for far vision, however (Markus, 1906; Reitsch, 1925; Holmes, 1931; Adie, 1932; Heersema and Moersch, 1939). The patient is unable to relax accommodation when looking from a close to a distant object - a symptom which has been termed spasm of accommodation. Spasm of

accommodation can also be induced in normal subjects by powerful parasympathomimetic drugs. It has already been mentioned that there is an increase in the sensitivity of the tonic pupil to the parasympathomimetic drug acetyl B methyl choline. These two facts suggest the possibility of an increased sensitivity of the ciliary muscle to parasympathomimetic drugs.

The defect of accommodation appears to follow the same course as that of the pupil in the Holmes-Adie syndrome - paralysis followed by a tonic reaction. It is reasonable therefore to enquire if, in the second stage, there is a restoration in the range of accommodation, and if it is accompanied by slowness of accommodation and sensitivity to parasympathomimetic drugs.

The following questions were asked:-

1. Is there a residual reduction in the range of accommodation of the eye with a tonic pupil?
2. Is there always a delay in accommodation for either near or distant vision?
3. Is the affected ciliary muscle more sensitive to parasympathomimetic drugs?

The answer to question 3 was obtained, but not to questions 1 and 2.

The Tendon Reflexes in the Holmes-Adie Syndrome

Partial loss of tendon reflexes - most commonly the knee and ankle jerks - has been reported by most authors since the classical descriptions of Markus (1906), Holmes (1931) and Adie (1932). Adie (1932) and Kennedy et al (1938) stated that loss of the upper limb reflexes is uncommon, but Graveson (1949) reported it in 8 of his 16 patients and a total loss of tendon reflexes in 3 cases.

The explanation of this areflexia remains unknown. Bolsi (1952) found slight but, he claimed, significant alterations in deep sensation of the limbs and a variety of bony deformities of the spinal column, to which he attributed the loss of reflexes. Kyrieleis (1951) denied that there is any disturbance of muscle tone. Domzal (1955) suggested that a mesencephalic lesion is responsible for both the absent tendon reflexes and the pupillary disorder. The tendon reflexes will not be discussed in this thesis.

CHAPTER III

PATIENTS AND NORMAL SUBJECTS EXAMINED

The following patients were examined:-

1. One patient with Horner's syndrome resulting from a bronchogenic carcinoma and one patient with a partial paralysis of the pupil from an oculomotor nerve palsy, in the investigation of complete denervation of the pupil (p.26).
2. Five patients with Horner's syndrome caused by central nervous lesions (p.33).
3. Ten patients with syphilitic pupils (p.46).
4. Twenty patients with the Holmes-Adie syndrome (p.48).

In addition, normal subjects or patients with normal eyes were tested as follows:-

1. Ten patients with atypical facial or brachial pain but with normal pupils, in the investigation of complete denervation of the pupil and the mode of action of cocaine (p.26 and p.29).
2. Six normal subjects in the investigation of the effect of cocaine on accommodation (p.40).
3. Four patients with Ménière's disease or facial pain but with normal accommodation, in the study of the effect of a sympathetic block on accommodation (p.42).
4. Fifteen normal subjects acting as controls for the patients with the Holmes-Adie syndrome (p.63).

CHAPTER IV

METHODS OF INVESTIGATION

In this chapter will be given details of the chief methods of investigation referred to later in the thesis.

MEASUREMENT OF PUPIL SIZE

The size of the pupil was measured by means of a simple Haab pupillometer, consisting of a series of graduated black circles for comparison with the pupil. Differences in diameter of $\frac{1}{4}$ mm. could be estimated with ease. Except where specifically stated, the Haab pupillometer was used for all estimates of pupil size. The entoptic pupillometer described by Cogan (1941) was found to be unsatisfactory, because the patient himself had to determine the end-point, and pupillary constriction to convergence could not be assessed accurately.

The size of the pupil at rest was measured with the subject looking at a distant object. The reaction to convergence was tested by asking the subject to fix his eyes on an object placed at his near point. If the patient was unable to maintain ocular convergence, no reliable estimate of the reaction to convergence could be made, because accommodation by itself does not provide an adequate stimulus to pupillary constriction (Kestenbaum, 1947). Care was taken to avoid differences in pupillary size resulting from variations in illumination. When the reaction to light was lost - in patients with syphilis or the Holmes-Adie syndrome - it was permissible to compare different patients under uncontrolled conditions of illumination.



Fig. 1 - Pupillographic Record of Patient with Tonic Pupil.

From above downwards, successive frames are shown at 4-second intervals. They depict the constriction of the pupil caused by convergence followed by slow pupillary dilatation.

A. The pupil before the stellate ganglion block.

B. The pupil after the stellate ganglion block.

But in normal subjects and in patients with Horner's syndrome, the lighting conditions were kept constant.

PUPILLOGRAPHY FOR TIMING THE TONIC REACTION OF THE

HOLMES-ADIE PUPIL

It was necessary in one patient to time with great accuracy the dilatation of the tonic pupil on relaxing convergence of the eyes, before and after a sympathetic block. A cinephotographic record of the pupil was therefore made. Illumination presented no problem, for this pupil did not react to even the brightest light. The patient was asked to look at a close object, and after the pupil had constricted to its fullest extent, she was told to look at the reflection of a distant light in a mirror placed close to the camera lens. A 16 mm. film was exposed at a rate of 16 frames per second and later projected on a screen, so that both time and pupil size could be measured with precision. Fig. 1 shows representative exposures at four-second intervals, before and after the sympathetic block.

THE STELLATE GANGLION BLOCK

A 1% solution of procaine hydrochloride was injected using an anterior cervical approach, according to the method advocated by Moore (1954). The patient lay in bed with his head supported on one pillow. A 19-gauge lumbar puncture needle was introduced at the level of the transverse process of the seventh cervical vertebra, and at the medial edge of the sterno-mastoid. The surface landmarks were two finger-breadths from the median plane and the same distance

above the clavicle. The carotid sheath was drawn laterally, and the needle inserted straight in until it met the side of the vertebral body. It was then withdrawn half a centimeter so as to inject the procaine superficial to the prevertebral muscles. The plunger of the needle was pulled back to ensure that no blood vessel nor the spinal theca had been entered, and 5 ml. of procaine were injected. An Horner's syndrome usually appeared within five minutes.

This technique was used on about fifty occasions without any complications. In particular, there resulted no case of pneumothorax, said to be the commonest mishap. On three occasions arterial blood was aspirated into the syringe, presumably from the vertebral artery; the needle was withdrawn for a fresh puncture. Some patients complained of discomfort or pain in the shoulder when the needle encountered the vertebral periosteum.

THE SWEAT TEST

A sweat test was required to assess if the Horner's syndrome caused by central nervous lesions was complete. It was also used in patients with the Holmes-Adie syndrome, when the effectiveness of a stellate ganglion block could not be gauged by observing the pupil.

The test was carried out by heating the patient under an electric cradle after the face, neck and ventral aspects of the trunk and limbs had been dusted with quinizarin 2:6 disulphonic acid powder (Burroughs and Wellcome). This powder turns purple on contact with moisture, serving as an indicator of the sweating areas of skin.

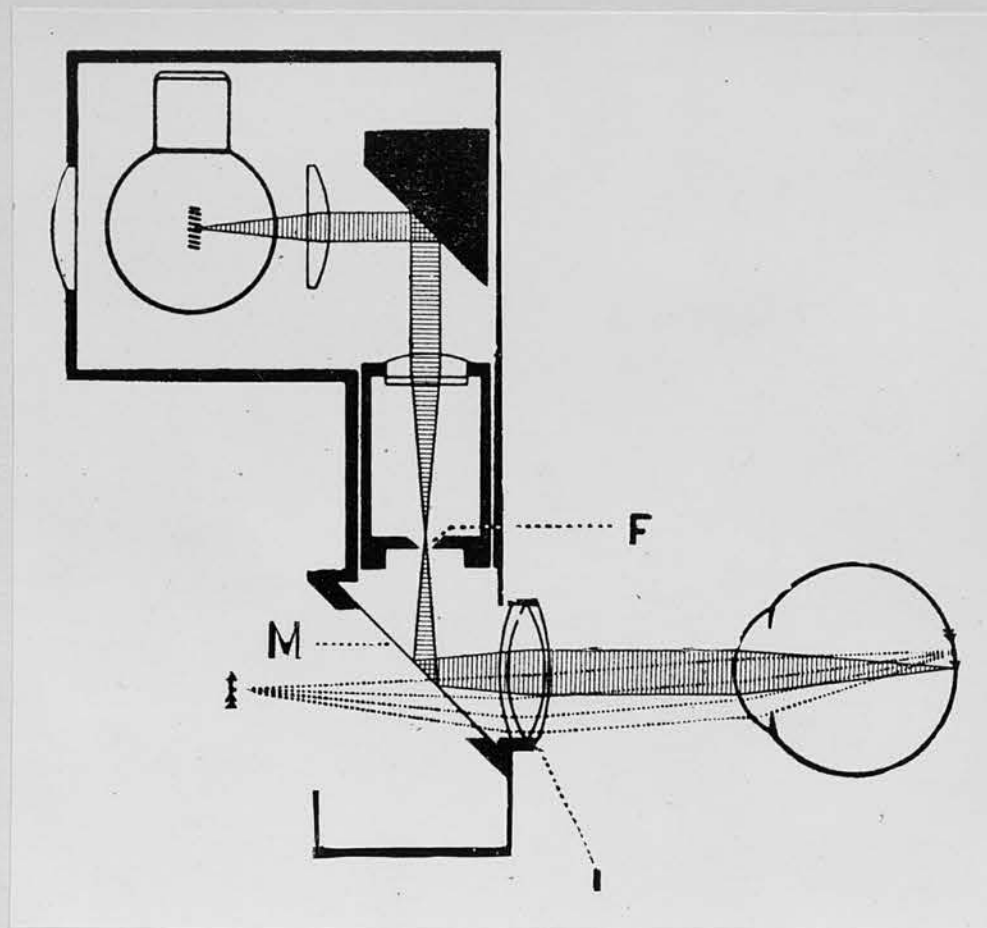


Fig. 3 - The System Controlling Accommodation

F is the fixation target. The beam of light leaving F is reflected by a pellicle mirror M, passes through the optometer lens L and enters the eye. The vergence of this beam of light is varied by altering the distance of F from the lens L. When F is at the principal focus of the lens L, the light rays entering the eye are parallel, so that the target is seen by an emmetropic eye only when accommodation is relaxed. When F is approximated to the lens, the light vergence increases and accommodation is stimulated.

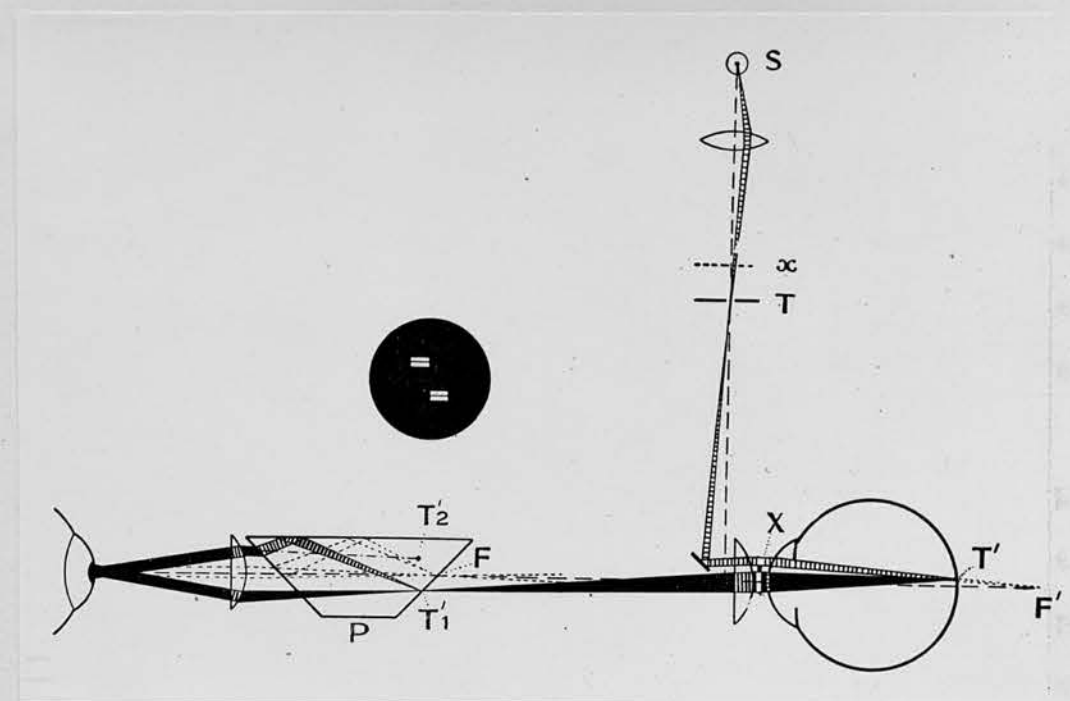


Fig. 2 - Principle of the Coincidence Optometer.

T is a linear target illuminated by a 36-matt lamp S. The beam of light enters the pupil at a fixed distance from the principal axis FF'. The image of T is projected on the subject's retina at T'. In the diagram, T' is slightly displaced from the principal axis. The reflected beam of light emerges from the eye and is intercepted by the prism P which reverses half the retinal image to an equal distance on the opposite side of the principal axis. If the subject's eye is ametropic, therefore, the observer will detect a separation of the two halves of the retinal image (T'1 and T'2). The observer will then adjust the position of T (e.g. to x) until the two halves of the image coincide. The required adjustment of T gives a measure of the refractive error.

MEASUREMENT OF REFRACTION AND OF ACCOMMODATION

Accommodation was measured by the difference in refraction of the eye caused by accommodating from distant to near vision. A modification of the coincidence optometer designed by Fincham (1937) was used, both for refracting the eye and for providing the stimulus to accommodation.

The refraction of the eye was measured objectively by viewing ophthalmoscopically the retinal image of an illuminated target consisting of a vertical line (Fig. 2). When the eye examined was ametropic, the retinal image fell to one or other side of the principal axis of the eye. This displacement could be seen through the observing system and corrected by altering the position of the target relative to an optometer lens. The required correction represented the refractive error which was read in dioptres on the scale carrying the moving target. The adjustment was made with precision by a coincidence setting.

The accommodation stimulus was provided by a second fixation target illuminated by a beam of light, the vergence of which could be varied (Fig. 3). When the light proceeding from the target was parallel, accommodation was relaxed; increasing divergence of light caused a corresponding increase in accommodation. This response is thought to depend on changes in chromatic aberration and on the normal scanning movements of the eye (Fincham, 1951). The fixation target consisted of a detailed black and white pattern which provided a good stimulus to accommodation (Fincham, 1957).

To avoid errors from spherical aberration and from astigmatism, the instrument was centred on the pupil and the same meridian was



Fig. 4 - The Retinal Image seen by the Observer

The two halves of the retinal image are out of alignment; the error of refraction depicted amounts to 0.50 dioptre.

TABLE I
Variation in the Measurement of Refraction with the
Coincidence Optometer

CASE	REFRACTION OF UNACCOMMODATED EYE (Dioptres)					
	Day 1	Day 2	Day 3	Day 4	Day 5	Mean
1	- 1.0	- 1.2	- 0.9	- 0.7	- 0.8	- 0.9
2	- 0.4	- 0.6	- 0.3	- 0.3	- 0.2	- 0.4
3	+ 0.1	+ 0.2	+ 0.3	+ 0.2	+ 0.3	+ 0.2
4	- 0.4	- 0.4	- 0.4	- 0.3	0	- 0.3

The refraction of the unaccommodated eye was measured on five consecutive days. The standard deviation of the readings was 0.14 dioptre.

used before each measurement. Alterations in size of the pupil are likely to cause changes of accommodation by themselves if there result any differences of light vergence. To overcome this important difficulty, the beam of light from the illuminating system was made to enter the pupil at a fixed distance from its centre; a constancy of size ($2\frac{1}{2}$ mm. diameter) of the "effective pupil" was thus ensured.

Fig. 4 shows how a change of 0.50 dioptre in the subject's refraction can be easily detected by the examiner. Fincham estimated the maximum error of his instrument, when used in practice, as about $1/8$ dioptre. In a series of four normal subjects, on each of whom the refraction of the relaxed eye was measured on four consecutive days, the standard deviation was 0.14 dioptre (Table I). Therefore, the change in refraction induced by a sympathetic block, for example, must be in the order of 0.3 dioptre (twice the standard deviation) before it is significant. In this work, refraction was estimated in tenths of a dioptre, but the experimental limitations of the tests were borne in mind before making any interpretations.

TIMING OF ACCOMMODATION

The method used for measuring the delay in accommodation for near vision was that recommended by Graveson (1949). The patient was asked to look at a distant object and then instructed to read a Jaeger test-card of a type which he could usually read comfortably (usually J4 to J8). The interval before the patient saw the print clearly was timed with a stopwatch, a mean of three readings being taken.

CHAPTER V

GENERAL PHYSIOLOGICAL PRINCIPLES GOVERNING THE NERVOUS CONTROL OF THE PUPIL AND ACCOMMODATION

In this chapter, the solution of certain physiological problems will be sought at a preliminary to the investigation of abnormalities of the pupil and accommodation. The three main problems, which will be formulated as hypotheses, are the following:-

- (1) What is the size of the pupil after complete interruption of its nervous control?
- (2) How does cocaine act on the pupil?
- (3) Does the sympathetic play any part in controlling normal accommodation?

- (1) THE SIZE OF THE PUPIL AFTER COMPLETE INTERRUPTION OF ITS NERVOUS CONTROL

HYPOTHESES

- a. When a pupil is dilated because of a parasympathetic lesion, additional interruption of the sympathetic innervation does not cause pupillary constriction.
- b. The miosis resulting from sympathectomy is dependent on normal parasympathetic function.

PREVIOUS WORK

It is usually stated that if a sympathetic lesion is superimposed on a parasympathetic one, the originally dilated pupil constricts. Thus, it is said that the miosis of the syphilitic pupil results from a sympathetic denervation being added to the parasympathetic lesion (Merritt and Moore, 1933). As a corollary,

TABLE II
Effect of Complete Denervation of the Pupil

CASE	AGE	SEX	SIDE	PUPIL SIZE (mm.)		
				At rest	After homatr. (2%)	After homatr. & symp. block
1	48	F	L	3	$\rightarrow 5\frac{1}{4}$	$\rightarrow 4\frac{3}{4}$
2	50	M	L	$4\frac{1}{4}$	$\rightarrow 6\frac{1}{4}$	$\rightarrow 5\frac{1}{2}$
3	75	F	R	$3\frac{1}{4}$	$\rightarrow 6\frac{1}{2}$	$\rightarrow 6\frac{1}{2}$
4	64	F	R	$3\frac{1}{2}$	$\rightarrow 7\frac{1}{2}$	$\rightarrow 7\frac{1}{4}$
5	52	M	R	$2\frac{3}{4}$	$\rightarrow 7\frac{3}{4}$	-
			L	$2\frac{1}{4}$	$\rightarrow 7\frac{3}{4}$	-

Cases 1 - 4 were subjects with normal pupils; a sympathetic block failed to cause any significant constriction of the homatropinized pupil.

Case 5 had a permanent Horner's syndrome on the left. Homatropine caused equal dilatation of the two pupils.

it is claimed that atropine fails to dilate a sympathectomized pupil. For example, Jaffe (1950) thought that homatropine only partially dilates the pupil in Horner's syndrome. Langworthy and Ortega (1943) disagreed with these views, however, and stated that complete denervation results in a dilated pupil. They reported that the human pupil assumes a resting size of 7 to 8 mm. when the sympathetic is cut and the parasympathetic paralysed with atropine. It was considered necessary to settle this argument before studying the syphilitic and Holmes-Adie pupils.

INVESTIGATIONS

Two investigations were carried out:-

1. Interruption of the sympathetic when the parasympathetic was completely paralysed.
2. Interruption of the sympathetic when the parasympathetic was only partly paralysed.

Investigation 1.

Method. - A temporary paralysis of the parasympathetic nerve endings was produced by instilling homatropine into the conjunctival sac; the stellate ganglion on the same side was then blocked with procaine. The resulting effect on the size of the pupil was observed.

Four patients with normal pupils had a sympathetic block for the treatment of atypical facial or brachial pain (Table II). The opportunity was taken of simultaneously observing the effect of homatropine. Drops of 2% homatropine hydrobromide were instilled into the conjunctival sac until the pupil ceased to react to bright torch light or to convergence. This required a period of about forty minutes. A stellate ganglion block was then performed. The pupil

could not serve as an indicator of whether or not the sympathetic block was effective, but ptosis and conjunctival injection were regarded as the decisive signs. The pupil was measured before and after administering the homatropine, and again after the procaine block.

One patient (Case 5) already had an Horner's syndrome caused by a bronchogenic carcinoma, so that the action of homatropine could be tested without the procaine block. The homatropine was introduced in both eyes in order to use the unaffected side as a control.

Results. - In two patients, the sympathetic block did not reduce the mydriasis caused by homatropine, and in three the pupil constricted by only $\frac{1}{4}$ to $\frac{3}{4}$ mm.

Investigation 2.

Method. - The sympathetic was blocked also in a patient with a partial paralysis of the pupil from a third nerve palsy, no homatropine being instilled.

Results. - The patient responded to the sympathetic block with a moderate pupillary constriction only (from $6\frac{1}{2}$ to $4\frac{1}{2}$ mm.). This constriction is less marked than the miosis induced in a normal eye by a stellate ganglion block, under comparable lighting conditions (Table III).

DISCUSSION AND CONCLUSIONS

The findings of Investigation 1 are in agreement with the observation of Langworthy and Ortega that the pupil devoid of both sympathetic and parasympathetic control is dilated; it measures $4\frac{3}{4}$ to $7\frac{3}{4}$ mm. Investigation 2 shows that decreased parasympathetic function allows only incomplete pupillary constriction when the

sympathetic is interrupted. The full miosis of Horner's syndrome is therefore dependent on an intact parasympathetic innervation. Thus may be rejected the belief that a sympathetic lesion can prevent full dilatation of the normal pupil when atropine is instilled. These conclusions will be referred to again in the discussion on the nervous control of the syphilitic pupil.

(2) THE MODE OF ACTION OF COCAINE ON THE PUPIL

HYPOTHESIS

When cocaine is instilled in the conjunctival sac, the resulting pupillary dilatation is dependent on intact sympathetic nerve endings; cocaine may be used as a test of damage to the sympathetic innervation, irrespective of the site of the lesion.

PREVIOUS WORK

The dilatation of the pupil that follows instillation of cocaine has been regarded as evidence of normal sympathetic function. Langworthy and Ortega (1943) and Apter (1954) applied this test to the investigation of syphilitic pupils; and Alajouanine and Morax (1938), and Scheie (1940) used it in the examination of Holmes-Adie pupils.

However, a recent study by Scheie and Ojers (1950) has thrown some doubt on the validity of this test. These authors claimed that cocaine, when injected into the anterior chamber of the eye of anaesthetised animals, causes pupillary dilatation even when the sympathetic nerve supply to the eye has been cut. They favoured a direct action of the drug in depressing the muscle cells of the iris; if correctly interpreted, they extended this explanation to the

action of cocaine instilled in the conjunctival sac. This is contrary to the opinion of Foerster and Gagel (1932) that locally instilled cocaine has no effect on the sympathectomized pupil. Moreover, Lenggenhager (1946) showed in three patients that cocaine loses its effect on the pupil when the sympathetic is blocked in the neck.

Even if it is accepted that cocaine fails to dilate the pupil when the peripheral sympathetic control is destroyed, there is a further question to be answered before applying this test clinically. Foerster and Gagel (1932), Wormser (1947), Jaffe (1950) and Pagliarani (1950) were unanimous in stating that the reaction of the pupil to cocaine is preserved in an Horner's syndrome when this syndrome is caused by a lesion in the central nervous system, and that the reaction is absent when the syndrome is caused by a lesion of the peripheral sympathetic system.

If this is correct, the reaction of an abnormal pupil to cocaine cannot be used as a test of sympathetic damage. In particular, a central nervous lesion has been postulated in both the syphilitic (Merritt and Moore, 1933) and the Holmes-Adie pupil (Adie, 1932). In these disorders, therefore, it would not be possible to interpret pupillary dilatation by cocaine as a sign of remaining sympathetic function. It was considered worthwhile enquiring into what determines this difference in reaction of the pupil; how does the Horner's syndrome caused by a central nervous lesion differ from that caused by a peripheral lesion?

Although recovery of function to a greater or lesser degree may follow a peripheral sympathectomy after an interval (Murray and

Thompson, 1957), the Horner's syndrome usually appears complete at first. In contrast, there is good evidence that Horner's syndrome which is due to a central nervous lesion is often incomplete from the beginning. Thus, List and Peet (1939) found partial preservation of sweating on the side of the lesion in their eighteen cases of disease of the pons, medulla or cervical spinal cord. Stead et al (1942) also reported incomplete Horner's syndromes in their six cases of vascular brain-stem lesions. These authors explained their findings by postulating a decussation of the autonomic pathways descending from the hypothalamus. For this there is some evidence as shown by Magoun et al (1938). It would therefore seem that the preservation of sweating was due to nerve fibres from the opposite hypothalamus crossing caudal to the lesion. The alternative explanation is that the autonomic pathways are so widely scattered within the brain-stem that their complete destruction only seldom takes place. The work of Magoun et al (1938) also substantiates the theory of a widespread distribution of the autonomic fibres in the brain-stem.

In addition, Stead et al (1942) observed that after lesions of the medulla in man, heating of the body might cause normal vasodilatation but only diminished sweating. They suggested therefore that the efferent autonomic tracts in the medulla were so distributed as to allow their selective destruction by disease.

Because autonomic-controlled functions may be only partly or selectively impaired by disease, it is possible that the partial preservation of the effect of cocaine in an Horner's syndrome of central nervous origin is due to the incomplete extent of the

TABLE III

Effect of Cocaine on the Pupil in the Presence of a
Sympathetic Block

CASE	AGE	SEX	SIZE OF PUPIL (mm.)			
			At rest	After cocaine (3%)	After cocaine & symp. block	After symp. block only
1	56	F	3	$\rightarrow 4\frac{1}{2}$	$\rightarrow 2\frac{1}{4}$	-
2	66	F	$4\frac{1}{2}$	$\rightarrow 6$	$\rightarrow 2\frac{3}{4}$	$\rightarrow 2\frac{3}{4}$
3	40	F	3	$\rightarrow 4\frac{1}{2}$	$\rightarrow 2\frac{1}{4}$	$\rightarrow 2\frac{1}{4}$
4	40	F	$5\frac{1}{2}$	-	$\rightarrow 3\frac{1}{2}$	-
5	75	F	4	$\rightarrow 6$	$\rightarrow 3\frac{1}{4}$	$\rightarrow 3\frac{1}{4}$
6	57	F	$3\frac{3}{4}$	$\rightarrow 4\frac{1}{2}$	$\rightarrow 3\frac{1}{4}$	-

Cocaine did not dilate the pupil when the stellate ganglion was blocked. In fact, cocaine had no action whatsoever when instilled in the presence of a sympathetic block (Cases 2, 3 and 5).

sympathectomy.

INVESTIGATIONS

Three investigations were undertaken:-

1. Does cocaine dilate the pupil or not, when the sympathetic innervation to the eye has been blocked with procaine?
2. Does cocaine dilate the pupil when the sympathetic innervation to the eye has been damaged by a central nervous lesion?
3. How complete is the sympathectomy resulting from a central nervous lesion?

Investigation 1. - Effect of Cocaine on the Pupil in the Presence of a Sympathetic Block.

Method. - Six patients with normal pupils had a stellate ganglion block for the treatment of atypical facial pain or brachial neuralgia (Table III). Two drops of a 3% solution of cocaine hydrochloride were first instilled into the conjunctival sac on the side of the proposed block. When maximal pupillary dilatation had resulted (usually after 20 minutes), a procaine sympathetic block was carried out as described on p.22. The pupil was measured before and after the administration of cocaine, and after the block had been judged to be effective; the classical signs of Horner's syndrome were easily ascertained.

In three patients (Cases 2, 3 & 5), the stellate ganglion block was repeated at a later date without the cocaine eye-drops, and the resulting pupillary constriction compared with that caused by the block and the eye-drops.

TABLE IV

Horner's Syndrome due to Central Nervous Lesions

CASE	AGE	SEX	DIAGNOSIS & DURATION OF ILLNESS	SIDE	SIZE OF PUPIL (mm.)			SWEAT TEST
					At rest	After cocaine (3%)	After stellate block	
1	51	F	Syringo- bulbia (20 years)	R	6	→ 8	-	Diminished but present on the left side
				L	5 $\frac{1}{4}$	→ 7	-	
2	35	F	Syringo- bulbia (10 years)	R	5 $\frac{3}{4}$	→ 7 $\frac{1}{2}$	-	Diminished but present on left side
				L	4 $\frac{1}{4}$	→ 5 $\frac{1}{2}$	-	
3	45	F	Right cervical cordotomy (2 weeks)	R	3 $\frac{3}{4}$	→ 5 $\frac{1}{4}$	→ 3 $\frac{1}{4}$	Diminished but present on right side
				L	4 $\frac{3}{4}$	→ 6 $\frac{3}{4}$	-	
4	64	F	Thrombosis of right post. inf. cereb. art. (2 weeks)	R	4 $\frac{1}{4}$	→ 5 $\frac{3}{4}$	→ 3 $\frac{1}{2}$	Diminished but present on right side
				L	5 $\frac{1}{4}$	→ 7 $\frac{1}{2}$	-	
5	41	M	Thrombosis of right sup. cereb. art. (2 $\frac{1}{2}$ years)	R	4 $\frac{1}{4}$	→ 7	-	Diminished but present on right side
				L	4 $\frac{3}{4}$	→ 7 $\frac{1}{2}$	-	

In every case cocaine eye-drops caused dilatation of the smaller pupil, though to a lesser degree than of the normal pupil. But the sympathetic lesion was incomplete as shown by the partial preservation of sweating on the abnormal side and the accentuation of the miosis by the sympathetic blocks in Cases 3 and 4.

Results. - The results are shown in Table III. The stellate ganglion block reversed the dilatation caused by the cocaine eye-drops, and the pupil usually became smaller than it had been before the test was begun. Similarly, the lid retraction due to the cocaine was replaced by a lid ptosis after the sympathetic block.

In cases 2, 3 & 5, the size of the pupil after both cocaine and the sympathetic block was identical with that produced by the sympathetic block alone. This indicates that when the sympathetic is interrupted, cocaine has no effect in dilating the pupil.

Investigation 2. - Effect of Cocaine on the Pupil in the Presence of Horner's Syndrome caused by a Central Nervous Lesion.

Method. - Five patients with Horner's syndrome were examined - four patients had brain-stem lesions and one patient had a lesion of the cervical cord. Details of age, sex, diagnosis and duration of illness are given in Table IV.

The size of the pupils was measured before, and twenty minutes after, 2 drops of cocaine hydrochloride (3%) had been instilled into the conjunctival sac of each eye. The same unstandardized pipette was used for each instillation.

Results. - In all cases, cocaine did cause pupillary dilatation on the side of the Horner's syndrome, but this effect was never greater than on the normal side (Table IV). In fact, the pupillary dilatation was reduced in comparison with the normal eye in Cases 1 to 4, and equal in Case 5.

Investigation 3. - Tests of Completeness of Horner's Syndrome caused by Central Nervous Lesions.

Methods. - A sweat test was carried out on the five patients

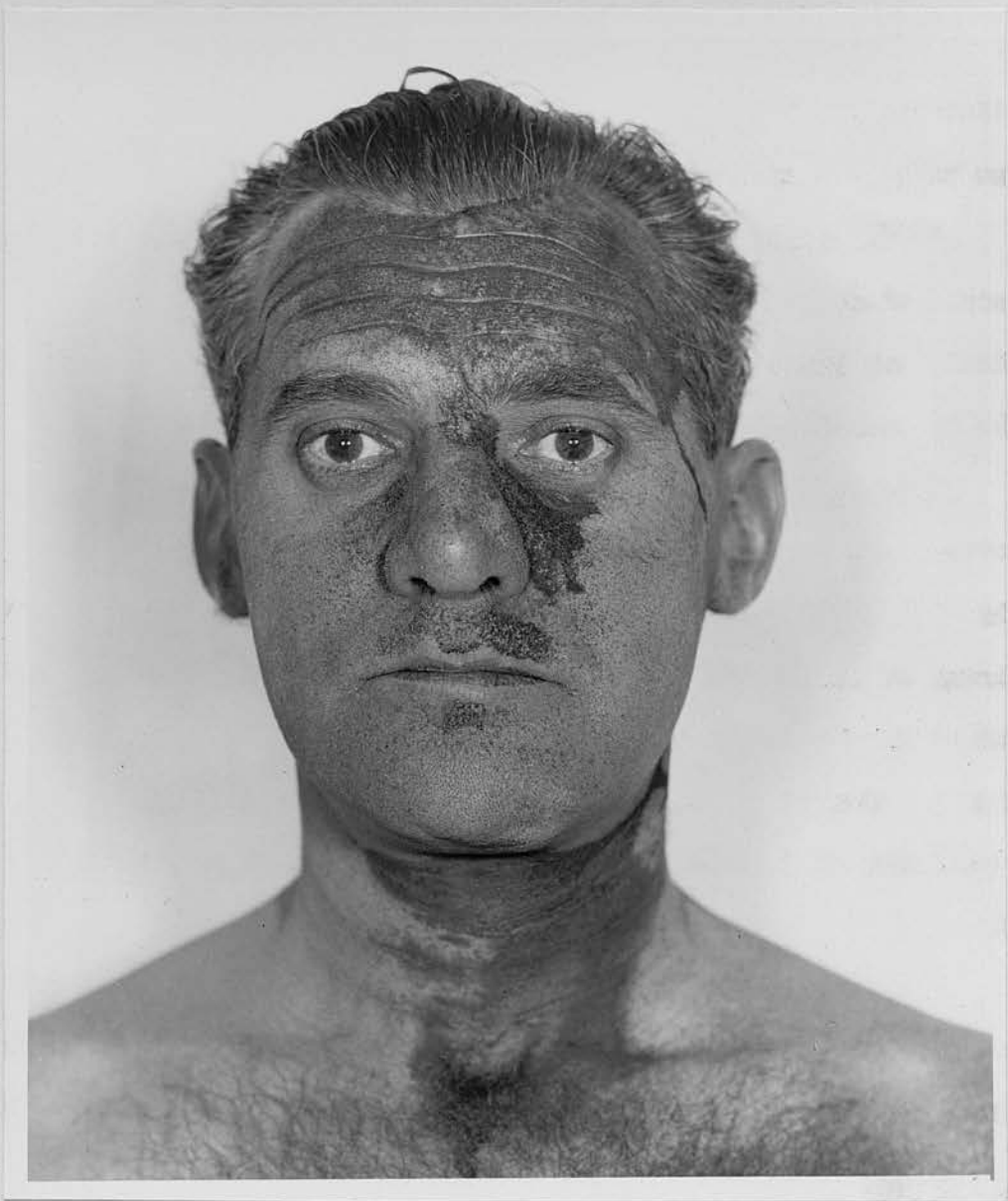


Fig. 5 - Sweating in Response to Heat in a Patient with right-sided Horner's Syndrome (Case 4).

The sweating areas are shown by the dark patches caused by the quinizarin turning purple on contact with moisture. Sweating was preserved, though diminished, on the right.

of the previous investigation, in whom cocaine caused pupillary dilatation on the side of the Horner's syndrome. The method used has been explained on p. 23.

In two patients (Cases 3 and 4), a stellate ganglion block was performed on the side of the Horner's syndrome to see if further miosis and ptosis could be induced by completing the interruption of the sympathetic innervation to the eye.

Results. - In none of the five patients was the sympathetic lesion complete, as shown by a partial preservation of sweating on the side of the lesion. Sweating was always present to some extent, though it was delayed and reduced on the abnormal side in the face and neck. The response in Case 4 was typical and is illustrated in Fig. 5. Over the trunk and limbs also, sweating was usually diminished on the side of the smaller pupil, but in two patients (Cases 4 and 5) sweating over the legs was symmetrical.

That the Horner's syndrome was only partial was further substantiated in Cases 3 and 4. In these patients, the stellate ganglion block accentuated the miosis and ptosis already present (Table IV).

DISCUSSION AND CONCLUSIONS

This study shows that the effect of locally instilled cocaine in causing pupillary dilatation is dependent on an intact sympathetic innervation. Certainly, the action of cocaine is lost when the peripheral sympathetic fibres are blocked with procaine. This finding is in keeping with the observations of Foerster and Gagel (1932) and Lenggenger (1946).

Yet it was confirmed that cocaine still causes pupillary dilatation in spite of an Horner's syndrome caused by central nervous

disease. But the important additional observation was made that in no case was the Horner's syndrome complete, as shown by the sweat tests. It is reasonable, therefore, to ascribe the preservation of the cocaine reaction to the partial damage of the sympathetic pathways from central nervous lesions. It may be objected that deductions from the sweating response as to the innervation of the iris are not valid, because there is evidence that the autonomic functions may be impaired selectively after brain-stem lesions (Stead et al, 1942). Direct evidence of the incomplete extent of the pupillary miosis and lid ptosis was therefore obtained by the stellate ganglion blocks. The observation of only partial sympathetic damage after central nervous lesions agrees with that of Magoun et al (1938), and List and Peet (1939). These workers ascribed the partial degree of the sympathetic interruption to decussations of the autonomic pathways in the central nervous system. An equally likely explanation is that these paths have a widespread representation in the brain-stem.

It is doubtful if the reaction of the pupil to cocaine helps in distinguishing between a central nervous and a peripheral lesion, as has been claimed by Foerster and Gagel (1932), Wormser (1947) and Jaffe (1950). For pupillary dilatation to cocaine has been described after peripheral sympathectomies (Pagliarani, 1950), presumably after recovery of function has occurred. The reaction to cocaine is more likely to bear a quantitative relation to the sympathetic innervation of the iris. Accordingly, cocaine will be used in the present study to determine the degree to which an abnormal pupil is still under sympathetic control.

The exact mechanism of the sympathomimetic action of cocaine is

unknown. Philpot (1940) suggested that it prevents the destruction of adrenaline by inhibiting amine oxidase, an enzyme which is probably responsible for the oxidation of adrenaline. Recent studies have revealed that cocaine also influences the action of 5-hydroxy tryptamine (Gaddum and Hameed, 1954); the action of 5-hydroxy tryptamine on sheep's carotid artery is increased, whereas that on guinea-pig's ileum is decreased. 5-hydroxy tryptamine has been found in cats to cause a slight initial dilatation of the pupil followed by marked constriction (Page, 1952). It is therefore possible to visualize a dependence of cocaine on 5-hydroxy tryptamine in causing pupillary dilatation. This supposition is entirely hypothetical, but it may prove rewarding to investigate further the interrelationship of these two substances.

(3) THE NERVOUS CONTROL OF ACCOMMODATION

INTRODUCTION

It is accepted that the third cranial nerve - through its parasympathetic component - regulates accommodation for near vision. Whether or not the sympathetic plays any part in the control of accommodation is still a question of controversy; recent opinion favours a definite but subsidiary function. Thus, Duke-Elder (1949) says:

"... it would appear that the sympathetic plays a minor inhibitory role in accommodation for near vision and a major and active role in accommodation for distance."

The existence of a sympathetic innervation of the iris is well established, and its contribution to the pathogenesis of pupillary

abnormalities will be studied in this thesis. Before approaching the problem of abnormal accommodation in the Holmes-Adie syndrome, it was considered essential to determine to what extent, if any, the sympathetic innervation controls normal accommodation. Evidence will be produced to show that there is no significant sympathetic control of the ciliary muscle.

PREVIOUS WORK

Of recent years there has grown a belief that the ciliary muscle consists of two more or less distinct bundles - the first of circular (muscle of Müller), and the second of meridional and radial smooth muscle fibres (muscle of Brücke). It has further been suggested that there is a mutually antagonistic innervation - parasympathetic nerve fibres from the oculomotor nerve to the circular bundle and sympathetic nerves to the meridional muscle (Byrne, 1933).

When Helmholtz (1909) formulated his theory of accommodation, he thought it "highly improbable" that the meridional fibres of the ciliary muscle could produce accommodation for far vision; his chief argument was that the circular and meridional fibre layers are too intermingled to allow a separate action. Thus, he rejected the suggestion put forward by Henke (1860) that there exists two antagonistic divisions to the ciliary muscle.

Somewhat conjectural arguments have been put forward in support of the hypothesis of a sympathetic innervation. The most popular of these is that the structures controlled by the autonomic nervous system have, as a rule, a dual nerve supply - sympathetic and parasympathetic (Cogan, 1937). On the basis of comparative anatomy, Henderson (1926) reasoned that the meridional muscle fibres must

subserve a useful function; they are, in fact, phylogenetically older than the circular fibres. Other workers (Henke, 1860; Warlomont, 1875) concluded from the morphological subdivision of the ciliary muscle that a double innervation is to be expected. Matteucci (1947), who found an innervation similar for the two types of bundle in the ciliary muscle, was more cautious; he believed that the presence of a true functional antagonism between the two parts of the muscle was not yet proven.

The reported results of animal experiments seemed to favour the presence of a subsidiary sympathetic control of accommodation. Olmsted is the main contributor in this field, and with other workers has published his findings in different species (Olmsted and Morgan, 1939; Morgan, Olmsted and Watrous, 1940; Olmsted and Morgan, 1941; Olmsted, 1944). He stimulated the cervical sympathetic in the presence of either intact or paralysed parasympathetic nerves to the ciliary muscle, and consistently obtained a change in refraction towards hypermetropia. This amounted to $2\frac{1}{2}$ dioptres in the rabbit, $6\frac{1}{2}$ dioptres in the cat, $1\frac{1}{2}$ dioptre in the monkey and seldom more than 1 dioptre in the dog. After removal of the ciliary ganglion, however, sympathetic stimulation failed to cause hypermetropia, a discrepancy which Olmsted attributed to long-continued inactivity of the circular fibres rendering the radial fibres ineffective. Cervical sympathectomy in the cat resulted in a change of refraction towards myopia. The eye was refracted by the observation, both visual and photographic, of the Purkinje images.

In contrast with the findings of Olmsted, Langley and Anderson (1892) were unable to detect with their phacoscopic method any

alteration in accommodation from stimulation of the cervical sympathetic chain in the dog, cat and rabbit. Kuntz et al (1946) also concluded from their experiments in cats that the efferent innervation of the ciliary muscle is wholly parasympathetic. They were usually unable to detect a dioptric change in the lens after stimulation of the cervical sympathetic. They found, however, that faradic stimulation of the sciatic nerve, used as a painful stimulus, induced an hypermetropia of 1 to $2\frac{1}{2}$ dioptries. They gave evidence that this effect was mediated by the parasympathetic fibres of the oculomotor nerve, but that these were adrenergic in type. Refraction was measured by skiascopy.

Investigations in man have consisted chiefly of observing the effect of sympathomimetic and sympatholytic drugs instilled into the conjunctival sac. The drugs most commonly used were cocaine and ergotamine: they have been reported to cause a slight degree of hypermetropia and myopia respectively (Graves, 1926; Poos, 1928; Heath, 1936; Cogan, 1937; Monjé, 1952; Siebeck, 1953; Alajmo, 1954; Meesmann, 1956; Van Lint and Alaerts, 1956). In addition, Poos claimed that adrenaline, locally instilled after a cervical sympathectomy, caused a decrease in accommodation in a way strictly analogous to the paradoxical dilatation of the denervated pupil.

Cases of Horner's syndrome caused by surgical operation or disease have also been studied, and it has usually been said that the near point is closer on the side of the sympathetic lesion than on the normal side (Cobb and Scarlett, 1920; Cogan, 1937; Monjé, 1952). Moreover, Monjé noted a delay in the relaxation of accommodation in these cases. However, Kuntz et al (1946) found that

painful stimuli similar to but milder than those used in their cats, sometimes failed to produce any response in humans, or at the most induced an hypermetropia of $\frac{1}{4}$ to $\frac{3}{4}$ dioptre. A variety of techniques have been used for estimating the changes in refraction in man - retinoscopy, measurement of the near point, and direct observation by slit lamp microscopy of the lenticular capsule in the aphakic eye (Graves, 1926).

In summary, most workers have claimed to show that there exists a sympathetic regulation of accommodation for far vision, and some have reported an influence on near vision as well. An acceptance of these conclusions led Hollwich (1952) to ascribe asthenopia to a disturbed balance of the parasympathetic and sympathetic control of accommodation, and Emmrich (1953) to accept sympathetic irritation as the cause of decreased accommodation on the side of an infected tooth, sinus or ear.

INVESTIGATIONS

If there is any sympathetic regulation of normal accommodation, stimulation or interruption of the sympathetic nerve supply to the eye should cause a change towards hypermetropia or myopia respectively.

Two investigations were therefore designed:-

1. Stimulation of the sympathetic nerve endings in the ciliary muscle by cocaine.
2. Interruption of the sympathetic chain by a stellate ganglion block.

Accommodation was measured with the coincidence optometer (p. 24).

Investigation 1. - Stimulation of the Sympathetic Nerve Endings.

Method. - It has already been shown that cocaine instilled into the conjunctival sac causes dilatation of the pupil by enhancing the

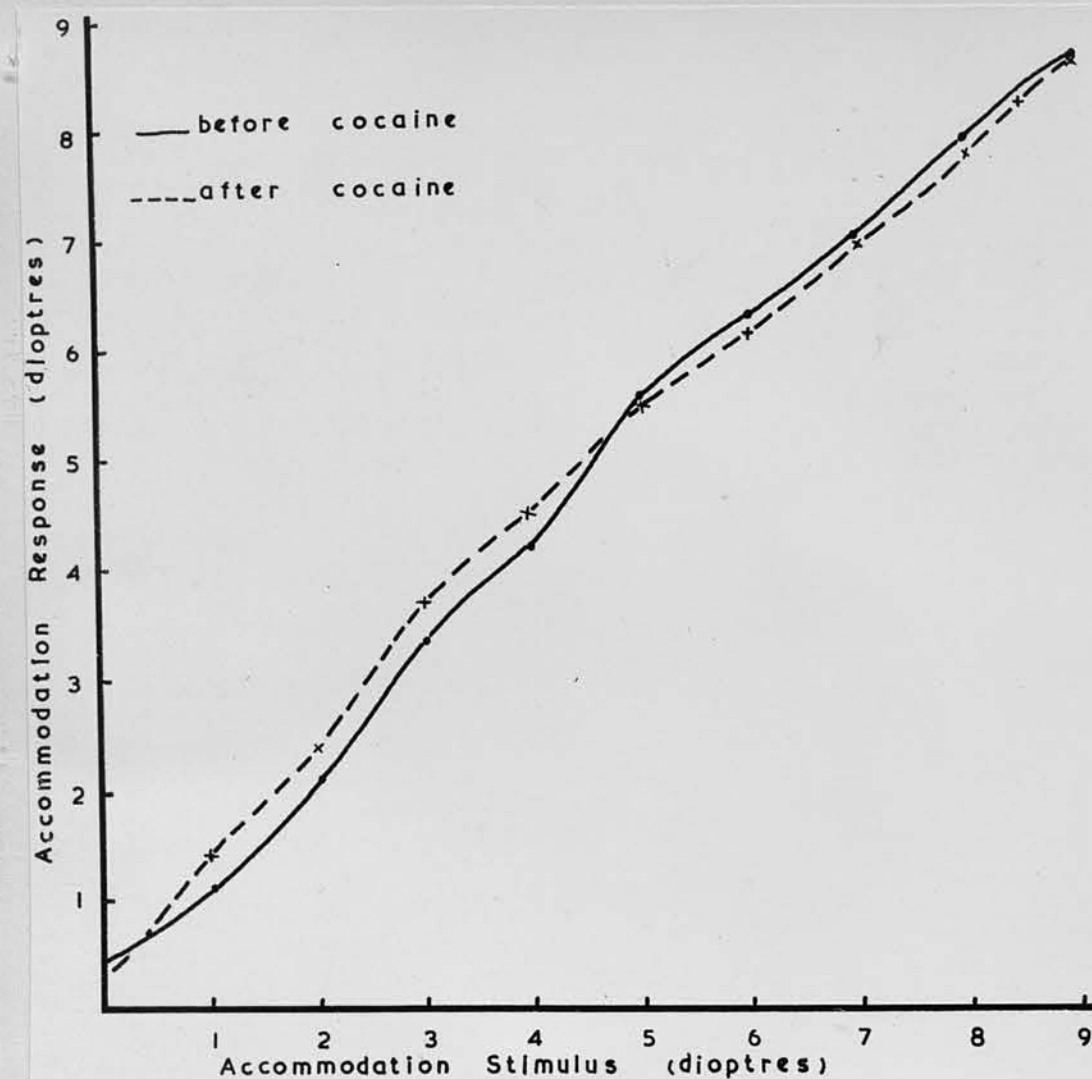


Fig. 6 - Accommodation before and after Instillation of Cocaine Hydrochloride (3%) in Case 2.

The refraction of the relaxed eye and the accommodation response hardly alter after cocaine.

TABLE VI
Effect of Cocaine on the Unaccommodated Eye

CASE	AGE	SEX	REFRACTION OF UNACCOMMODATED EYE (Dioptries)		
			Before cocaine *	After cocaine	Effect of cocaine
1	25	F	- 0.9	- 1.0	- 0.1
2	20	F	- 0.4	- 0.2	+ 0.2
3	21	F	+ 0.2	+ 0.3	+ 0.1
4	22	F	- 0.3	- 0.3	0
Mean effect of cocaine					+ 0.05

* Mean of five readings on consecutive days in each subject.

The action of cocaine was to induce only 0.05 dioptre of hypermetropia on the average, which is not significant.

TABLE V
Effect of Cocaine on the Unaccommodated and the Accommodated Eye

CASE	AGE	SEX	REFRACTION OF UNACCOMMODATED EYE (Dioptries)			REFRACTION OF FULLY ACCOMMODATED EYE (Dioptries)		
			Before cocaine	After cocaine	Effect of cocaine	Before cocaine	After cocaine	Effect of cocaine
1	25	F	- 1.0	- 1.3	- 0.3	- 10.0	- 10.3	- 0.3
2	20	F	- 0.7	- 1.1	- 0.4	- 10.1	- 10.5	- 0.4
3	21	F	0	- 0.5	- 0.5	- 7.8	- 8.0	- 0.2
4	22	F	- 0.4	- 0.3	+ 0.1	- 8.8	- 8.5	+ 0.3
5	26	M	+ 0.2	+ 0.1	- 0.1	- 5.5	- 5.5	0
6	24	F	- 1.3	- 1.5	- 0.2	- 9.0	- 9.1	- 0.1
Mean difference due to cocaine					- 0.23	Mean difference due to cocaine		- 0.12

Cocaine caused an average myopia of 0.23 dioptre in the unaccommodated eye, and of 0.12 dioptre in the accommodated eye. These changes are not significant.

normal sympathetic activity. It will be assumed that if enough of the drug is absorbed to act on the iris, it will also reach the ciliary muscle. The refraction and accommodation of six normal volunteers aged 20 to 26 years were tested before and after administering the drug (3 drops of 3% solution). As previous workers have alleged that the major role of the sympathetic innervation is to facilitate relaxation of accommodation, particular attention was paid to the effect of cocaine on the refraction of the eye accommodated for distant vision. In four subjects care was taken to allow for any daily variation and technical error by measuring the refraction of the relaxed eye on five consecutive days. The mean of the values for each eye was compared with the refraction after the administration of cocaine.

Results. - In Table V are shown the effects of the local instillation of cocaine on the refraction of the eye accommodated for distant and close vision. There was no consistent change towards hypermetropia among the six subjects. In fact, what little change took place was in the direction of myopia (a mean of 0.23 dioptre for distant vision and of 0.12 dioptre for close vision).

Table VI shows the results in the four subjects in whom the response to cocaine of the eye accommodated for distant vision was tested more accurately. The mean change induced by cocaine was only 0.05 dioptre of hypermetropia. It has already been shown (p.25) that only differences greater than 0.30 dioptre could be accepted as outside the limits of experimental error. Fig. 6 shows how little alteration was caused in the accommodative response after the instillation of cocaine.

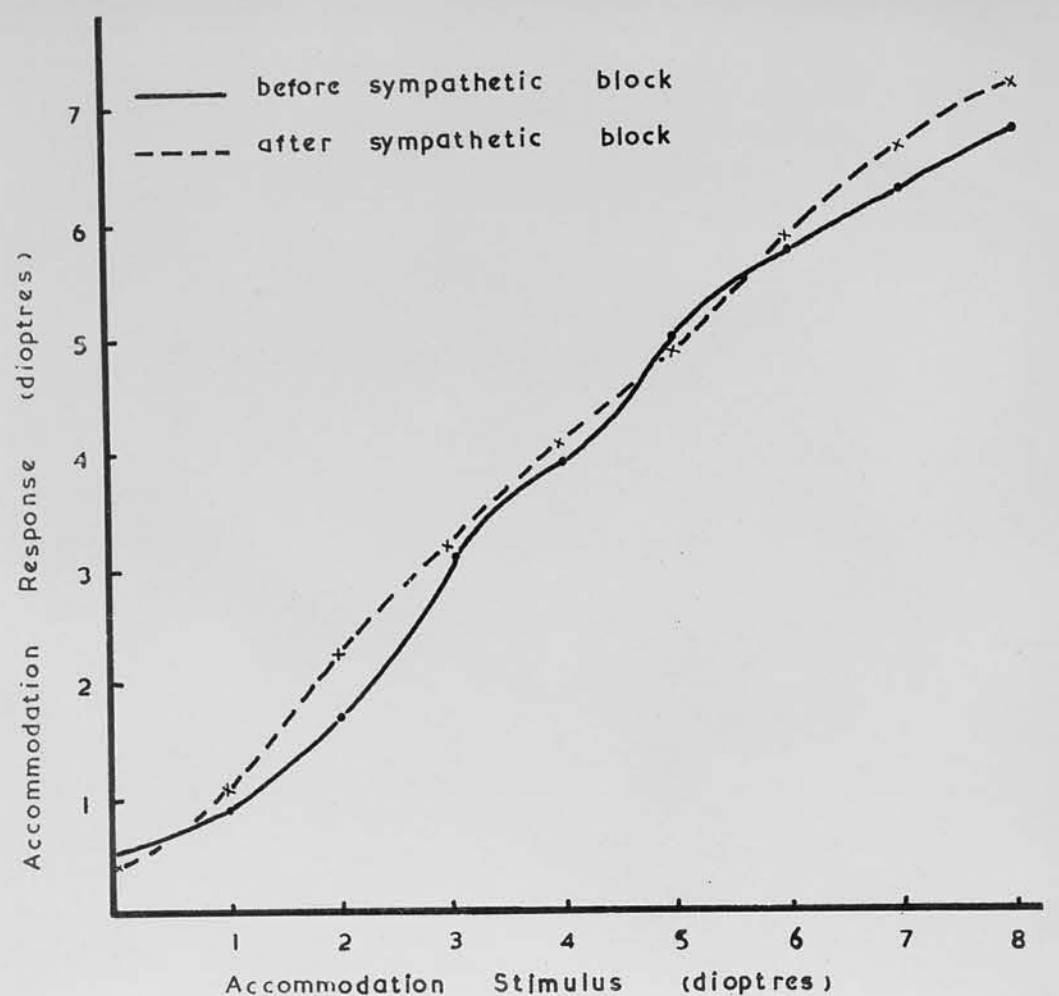


Fig. 7 - Accommodation before and after Stellate Ganglion Block (Case 4).

The refraction of the relaxed eye and the accommodation response hardly alter after the stellate ganglion block.

TABLE VII
Effect of Sympathetic Block on the Unaccommodated and the Accommodated Eye

CASE	AGE	SEX	REFRACTION OF UNACCOMMODATED EYE (Dioptries)			REFRACTION OF FULLY ACCOMMODATED EYE (Dioptries)		
			Before block	After block	Effect of block	Before block	After block	Effect of block
1	33	F	+ 3.5	+ 3.8	+ 0.3	+ 0.1	+ 0.9	+ 0.8
2	45	M	+ 0.1	+ 0.2	+ 0.1	- 0.9	- 0.9	0
3	31	F	- 1.2	- 1.1	+ 0.1	- 4.0	- 3.6	+ 0.4
4	25	F	- 0.5	- 0.4	+ 0.1	- 7.0	- 7.2	- 0.2
Mean difference due to block					+ 0.15	Mean difference due to block		+ 0.25

A sympathetic block caused an average hypermetropia of 0.15 dioptre in the unaccommodated eye, and of 0.25 dioptre in the accommodated eye. These changes are not significant.

Investigation 2. - Interruption of the Sympathetic Chain by
Stellate Ganglion Block.

Method. - The stellate ganglion block was performed as described on p.22. Ideally, young subjects with a large range of accommodation should have been chosen for this examination, but the choice was restricted to four patients suffering from non-ocular disorders which justified the use of this procedure in treatment or investigation (i.e. Ménière's disease and facial pain). Their ages ranged from 25 to 45. The most significant findings were obviously in the youngest subject in whom sclerotic changes in the lens were least advanced. Refraction and accommodation of the eye were measured before and after the sympathetic block; the refraction with accommodation relaxed was again considered to be the more important test.

Results. - Table VII shows the refraction of the eye accommodated for far and near vision, before and after a block of the stellate ganglion. There was no consistent change towards myopia. Instead, a slight hypermetropia was induced - a mean of 0.15 dioptre for distant vision, and of 0.25 dioptre for close vision. Neither of these changes is significant. Subject 4 had the largest range of accommodation and Fig. 7 illustrates how little it was altered by the sympathetic block.

DISCUSSION AND CONCLUSIONS

No significant change in the refraction of the eye - during either distant or close vision - resulted from stimulation or blocking of the sympathetic nerve supply to the eye. These findings indicate that the sympathetic cannot play an important role in the control of accommodation.

It is difficult to account for the discrepancy between the findings in this thesis and those of the majority of previous investigations. This study has the advantage of dealing with human subjects, in whom the tests could be controlled; the refraction was compared before and during the alteration of sympathetic activity (stimulation or interruption). Moreover, an accurate method of measuring refraction was used, and its limitations were ascertained before undertaking the tests. The disadvantage of varying pupillary size by the test procedure was overcome by maintaining the "effective pupil" constant.

As there is no sympathetic control of normal accommodation, it is proposed to consider accommodation as controlled entirely by the parasympathetic innervation. Thus may be dismissed the possibility that the sympathetic innervation plays any part in the pathogenesis of abnormal accommodation, such as in the Holmes-Adie syndrome.

CHAPTER VI

INVESTIGATION OF THE PUPIL AND ACCOMMODATION IN DISEASE

THE SYPHILITIC PUPIL

DEFINITIONS

The term "Argyll Robertson sign" has given rise to considerable confusion, and its use will be omitted from this discussion; the pupillary abnormalities occurring in syphilis will be described in terms of pupil size and reaction to light and convergence. "Miosis" will refer to a pupillary diameter of 3 mm. or less.

HYPOTHESIS

The miosis of the classical syphilitic pupil and the ptosis which often accompanies it are not due to an interruption of the sympathetic innervation of the eye.

PREVIOUS WORK

It was seen in the general account of the literature that a lesion of the sympathetic is commonly held to be responsible for both the miosis and the failure of pupillary dilatation with atropine. It is certainly incorrect to argue that interruption of the sympathetic can prevent the full action of atropine - this was demonstrated earlier in this thesis by testing the effect of homatropine in subjects with Horner's syndrome (p. 26). No matter whether the sympathetic lesion results from disease or from a procaine block, the pupil dilates fully or almost fully under the influence of the drug.

In spite of the general acceptance of the hypothesis of sympathetic damage, there has been only little experimental work to

test it. Magoun and Ranson (1935) damaged the "pretectal region" in cats; they were unable to reproduce the "Argyll Robertson pupil" - miosis and isolated reflex paralysis to light. Extensive destruction of this region caused a total reflex paralysis of the pupil. Miosis was only seen during a short initial period, and was ascribed by these workers to irritation caused by the lesion; additional bilateral cervical sympathectomy failed to cause a miosis. Spiegel and Scala (1936) also failed in their attempts to produce the "Argyll Robertson pupil" experimentally. They made a unilateral section of the posterior commissure and destroyed the "pupillo dilator pathways", thus simulating the lesion postulated by Merritt and Moore (1933). They observed only moderate impairment of the light reflex and slight constriction of the pupil. When the pupil was treated with atropine, it dilated fully, if somewhat more slowly.

Investigations in man have been far less conclusive, and largely limited to testing the response of the miotic pupil to sympathomimetic substances instilled in the conjunctival sac. Bramwell (1924), Langworthy and Ortega (1943), and Apter (1954) found that the normal response of dilatation with cocaine was impaired or lost. When it did occur, however, there was a partial return of the light reflex, a phenomenon also observed by Myerson and Than (1938), who used benzedrine sulphate as their test substance. In contrast, Lowenstein (1956) thought that the dilatation resulting from cocaine was normal, as measured by his technique of pupillography. There is only one report of the effect of a sympathectomy in a patient with syphilitic optic atrophy, in whom the reaction to light was lost (Alajouanine, 1935). In this case too, a return of the reaction to

TABLE IX

Effect of Cocaine Hydrochloride (3%) on Syphilitic Pupils

CASE	SIDE	SIZE OF PUPIL (mm.)	
		Before Cocaine	After Cocaine
1	R L	$5\frac{1}{4}$ $5\frac{3}{4}$	$\rightarrow 7\frac{1}{4}$ $\rightarrow 7\frac{1}{2}$
2	R L	$4\frac{1}{4}$ $5\frac{1}{2}$	$\rightarrow 5\frac{3}{4}$ $\rightarrow 6$
3	R L	$7\frac{1}{4}$ 4	$\rightarrow 8$ $\rightarrow 5$
4	R L	$4\frac{1}{2}$ $3\frac{1}{2}$	$\rightarrow 5\frac{1}{2}$ $\rightarrow 5\frac{1}{2}$
5	R L	$3\frac{1}{2}$ 3	$\rightarrow 4\frac{1}{4}$ $\rightarrow 4\frac{1}{2}$
6	R L	$2\frac{1}{2}$ $3\frac{1}{4}$	$\rightarrow 3\frac{3}{4}$ $\rightarrow 5\frac{1}{2}$
7	R L	$3\frac{1}{4}$ $2\frac{1}{4}$	$\rightarrow 6$ $\rightarrow 3\frac{1}{2}$
8	R L	$2\frac{1}{2}$ 2	$\rightarrow 5$ $\rightarrow 3\frac{1}{4}$
9	R L	$2\frac{1}{4}$ $2\frac{1}{4}$	$\rightarrow 3\frac{1}{2}$ $\rightarrow 3\frac{1}{4}$
10	R L	$1\frac{3}{4}$ $1\frac{1}{2}$	$\rightarrow 2\frac{1}{2}$ $\rightarrow 2\frac{1}{4}$

Cocaine caused some dilatation of the pupil in every case.

TABLE VIII

Clinical Findings in Ten Patients with Syphilitic Pupils

CASE	AGE	SEX	CLINICAL FEATURES	W.R.		SIDE	REACTION TO LIGHT (mm.)	REACTION TO CONVERG.	PTOSIS
				BLOOD	C.S.F.				
1	56	M	Tabes dorsalis; bilateral 6th nerve palsies	+	-	R L	0 0	+ +	+ ++
2	68	F	Tabes dorsalis; extensor plantar responses	+	-	R L	0 $\frac{1}{2}$	0 +	- -
3	41	F	Tabes dorsalis	+++	+++	R L	$\frac{1}{2}$ $\frac{1}{4}$	++ ++	- -
4	69	F	Tabes dorsalis; optic atrophy	-	-	R L	$\frac{1}{4}$ $\frac{1}{4}$	++ ++	+ -
5	58	F	Meningo-vascular syphilis; brain-stem thrombosis	+	-	R L	0 0	+ ++	- -
6	65	M	Tabo-paresis	+	+++	R L	0 0	+ ++	- -
7	68	F	Facial anaesthesia; lightning pains and areflexia	-	-	R L	$\frac{1}{2}$ 0	++ +	+ +
8	64	M	Tabes dorsalis	-	+	R L	$\frac{3}{4}$ $\frac{1}{4}$	++ ++	- -
9	59	F	Vascular disease	+	-	R L	0 0	++ ++	- -
10	49	F	Tabes dorsalis	+++	-	R L	0 0	+ +	- -

The reaction to light (as tested with a torch light) was lost or markedly impaired in every case. The reaction to convergence is shown as brisk (++), impaired (+) or absent (0).

light was observed.

INVESTIGATIONS

The ten patients selected for study had varying abnormalities of the pupils considered to be due to syphilis in every case. The diagnosis was established either by a positive Wassermann reaction, or by unequivocal clinical evidence. (Table VIII) All ten patients had bilaterally abnormal pupils. Two investigations were designed to ascertain the degree to which the syphilitic pupil remains under sympathetic control.

Investigation 1.

Method. - The reaction to the conjunctival instillation of cocaine hydrochloride (2 drops of 3% solution) was tested in the twenty syphilitic pupils. It has already been shown that this reaction may be used as a test of remaining sympathetic innervation (p. 29).

Results. - Table IX shows that in no case was the reaction to cocaine completely lost, but dilatation of the pupil amounted to only 1 mm. or so in Case 9, and $\frac{3}{4}$ mm. in Case 10.

Investigation 2.

Method. - The effect of a stellate ganglion block was observed in nine syphilitic pupils. It was argued that if the block resulted in pupillary constriction, at least some sympathetic fibres must have been functioning. Moreover, if miotic syphilitic pupils really are the result of sympathetic destruction, a sympathetic block should convert a larger syphilitic pupil into a miotic one (3 mm. or less). Blocking of the stellate ganglion has not hitherto been applied to

TABLE X

Effect of Sympathetic Block on Syphilitic Pupils

CASE	SIDE	SIZE OF PUPIL (mm.)	
		Before sympathetic block	After sympathetic block
1	R	$5\frac{3}{4}$	$\rightarrow 4\frac{3}{4}$
	L	$5\frac{3}{4}$	$\rightarrow 4$
2	R	$4\frac{1}{2}$	$\rightarrow 3\frac{1}{4}$
3	R	$5\frac{1}{4}$	$\rightarrow 4\frac{1}{4}$
4	R	$3\frac{3}{4}$	$\rightarrow 3\frac{1}{4}$
5	L	3	$\rightarrow 2\frac{3}{4}$
7	L	2	$\rightarrow 1\frac{1}{2}$
8	L	2	$\rightarrow 1\frac{3}{4}$
9	L	2	$\rightarrow 1\frac{1}{2}$

The sympathetic block caused some constriction of the pupil in every case.

syphilitic pupils as a method of investigation.

Results. -- The sympathetic block produced a reduction in size of all pupils, including the smallest (Table X). Cases 1 to 4 had relatively large pupils and the stellate ganglion block failed to constrict them to less than $3\frac{1}{2}$ mm. (It must be noted that in Cases 1 and 2 the reaction to convergence was markedly impaired, but in Cases 3 and 4 it was intact.)

In the four instances (Cases 1, right and left; 4 and 7) where there was a pre-existent ptosis, the procaine block accentuated it.

DISCUSSION

All the syphilitic pupils examined could be altered in size by modifying sympathetic activity. Stimulation by cocaine eye-drops caused dilatation, whereas interruption by a stellate ganglion block induced constriction of the pupil. It must be concluded that in these cases of syphilitic pupils, the sympathetic innervation to the eye must be partially preserved at least.

Admittedly, the dilatation caused by cocaine and the constriction resulting from the sympathetic block were least in the miotic pupils. In these pupils therefore, the sympathetic control may not have been wholly spared. But there is further evidence that a sympathetic denervation cannot be the cause of the miosis; for had it been, a large syphilitic pupil should have been convertible into a miotic one simply by performing a sympathetic block. This result was not obtained (Cases 1 to 4). In Cases 1 and 2 a response to the stellate ganglion block was not to be expected anyway, because the reaction to convergence was reduced and the pupils were approaching a state of complete denervation. It has been shown (p. 26) that such totally

TABLE XI

Clinical Findings in Twenty Patients with Holmes-Adie Syndrome

CASE	AGE	SEX	HISTORY	CLINICAL FEATURES	TRIDON REFLEXES	WASSERMANN REACTION
1	33	F	Sudden blurred vision (Dec. 1954)	Fixed irregular left pupil with slow accommodation	Normal	Negative in blood and C.S.F.
2	25	F	Sudden blurred vision on the left (1954) and on the right (1955). Diplopia and headaches	Bilateral changes affecting both pupil and accommodation - paralytic on the right and tonic on the left	All absent except right B.J.	Negative in blood and C.S.F.
3	37	F	Sudden blurred vision (1954)	Irregular tonic pupil with slow accommodation on the right	Right K.J. and left A.J. sluggish	Negative in blood
4	56	F	Blurred vision (1924)	Oval tonic left pupil	Absent T.J.s, K.J.s and A.J.s	Negative in blood
5	56	F	Incidental finding (1956)	Bilateral irregular tonic pupils	Absent A.J.s	Negative in blood
6	36	F	Incidental finding (1954)	Irregular tonic left pupil; normal accommodation	All absent	Negative in blood
7	69	F	Incidental finding (1955)	Bilateral irregular tonic pupils	T.J.s, K.J.s and A.J.s absent; S.J.s sluggish	Negative in blood and C.S.F.
8	34	F	Incidental finding (1955)	Bilateral irregular tonic pupils and slow accommodation on left	Absent T.J.s, K.J.s and A.J.s	Negative in blood
9	42	M	Delayed accommodation and unequal pupils (1951)	Bilateral irregular tonic pupils and slow accommodation	Absent A.J.s	Negative in blood
10	43	M	Sudden blurred and double vision (1956)	Bilateral irregular tonic pupils and slow accommodation	Normal	Negative in blood
11	37	F	Incidental finding (1956). Delayed accommodation	Bilateral irregular tonic pupils and slow accommodation	Absent B.J.s, T.J.s, K.J.s and A.J.s	Negative in blood
12	55	F	Incidental finding (1955). History of delayed accommodation	Bilateral irregular tonic pupils	All absent	Negative in blood and C.S.F.
13	57	F	Incidental finding (1956)	Irregular tonic right pupil	Absent A.J.s	Negative in blood and C.S.F.
14	51	F	Sudden blurred vision; dilated pupil (1955)	Irregular tonic left pupil and slow accommodation	Absent T.J.s, K.J.s, A.J.s and left S.J.	Negative in blood and C.S.F.
15	35	M	Sudden blurred and double vision; glare (1954)	Fixed left pupil; tonic pupil and slow accommodation one year later	Absent S.J.s and A.J.s; K.J.s sluggish	Negative in blood
16	19	F	Sudden ocular pain on the right; enlarged left pupil noted (1955)	Bilateral irregular tonic pupils; normal accommodation	Absent K.J.s and A.J.s	Negative in blood and C.S.F.
17	37	F	Incidental finding (1955)	Bilateral irregular tonic pupils; normal accommodation	Absent K.J.s, A.J.s and right B.J. and S.J.	Negative in blood and C.S.F.
18	49	M	Incidental finding (1955)	Irregular tonic pupil and slow accommodation on the right	Absent A.J.s	Negative in blood and C.S.F.
19	22	M	Delayed accommodation and unequal pupils (1954)	Bilateral irregular tonic pupils and slow accommodation	All absent except B.J.s	Negative in blood
20	51	M	Incidental finding (1955); glare	Oval tonic pupil, ptosis and facial anhidrosis on the left	A.J.s sluggish	Negative in blood and C.S.F.

B.J., S.J., T.J., K.J., A.J. = biceps, supinator, triceps, knee and ankle jerk.

paralysed pupils do not constrict after a sympathetic block. In Cases 3 and 4, however, the reaction to convergence was preserved; the pupils were therefore free to constrict once the influence of the sympathetic innervation had been removed. Yet they failed to do so, the smallest size reached being $3\frac{1}{2}$ mm.

In conclusion, a large syphilitic pupil cannot be transformed into a miotic one by complete interruption of the sympathetic innervation. In any case, there is evidence of partial preservation of sympathetic function in the miotic pupils of syphilis. It was also shown that the presence of ptosis associated with a syphilitic pupil is compatible with remaining sympathetic function, for a sympathetic block caused an accentuation of the ptosis. Even if a lesion of the sympathetic innervation is present to a partial degree, it cannot be held responsible for the miosis of the syphilitic pupil, and is unlikely to be the cause of the associated ptosis.

THE HOLMES-ADIE SYNDROME

Clinical Data

The relevant clinical features of twenty patients with the Holmes-Adie syndrome, seen over the course of three years, will now be discussed. Details of age, sex, symptoms, pupillary abnormalities, tendon reflexes and Wassermann reaction are shown in Table XI.

The series comprised 14 women and 6 men. As far as could be ascertained, the age of onset varied from 19 to 49 years. There was no evidence of a syphilitic basis in any of these patients; Wassermann reactions on the blood and cerebrospinal fluid were all negative. The histories of four cases of particular interest will

now be outlined (for further details, see Appendix). They illustrate the multiplicity of the pupillary abnormalities encountered and the common clinical course of the syndrome.

Cases 1 and 15 presented with unilateral internal ophthalmoplegia. After an interval of several weeks, Case 1 developed tonic accommodation and Case 15 a tonic pupil with slow accommodation. Case 2 was observed during a period of two and a half years; in turn she developed a left tonic pupil with loss of knee and ankle jerks, a fixed right pupil with a further loss of tendon reflexes in the arms, and finally bilateral tonic pupils. The accommodation in both eyes was also abnormal. Case 20 showed the rare combination of Horner's syndrome and a tonic pupil; only one similar case is reported in the literature (De Morsier and Franceschetti, 1953).

In 7 patients, the condition had been asymptomatic, but the other patients complained of the following symptoms:-

1. Glare (2 patients).
2. Blurring of vision (6 patients).
3. Double vision (3 patients).
4. Delayed accommodation (12 patients).
5. Ocular pain (1 patient).

Blurring of vision occurred usually at the onset of the disorder, whereas delayed accommodation persisted for months or years. Double vision was caused by muscular imbalance of the eyes.

All the clinical features emphasized by previous authors were encountered. The most reliable diagnostic sign was found to be delayed dilatation of the pupil after relaxation of convergence, a delay of 8 seconds or more being accepted as definitely abnormal

(Alajouanine and Morax, 1938). Pupillary constriction to convergence was always greater than to light or accommodation. An exception to this rule sometimes occurred in patients with an insufficiency of convergence, often associated with an heterophoria, as in Case 2. Bilateral pupillary changes were present in 11 out of the 20 cases. In Cases 7, 8, 12 and 16 there was only a slight delay in dilatation of the second pupil (6, 4, 7 and 5 seconds respectively), but there was additional evidence of abnormality for the outline of the pupil was irregular. The abnormal pupil was always irregular but not necessarily enlarged - in nine eyes it measured 4 mm. or less in diameter.

The effect of weeping on the tonic pupil was observed in one patient who was depressed (Case 12). As noted by Holmes (1931), Adie (1932) and Graveson (1949), crying caused pupillary constriction followed by a slow dilatation. In another patient who was given electro-convulsive therapy (Case 13) marked constriction of the abnormal pupil accompanied the tonic phase of the fit, and was followed by delayed relaxation. This is in contrast with the reported absence of any response to electro-convulsive therapy (Klein and Early, 1948).

In 14 eyes there appeared to be a delay in accommodation for near vision as measured by Graveson's clinical method (see p. 62).

Absence of some tendon reflexes was the rule, and was found in the upper as well as the lower limbs in 11 patients. In 2 patients (Cases 6 and 12), all the reflexes were lost. In only two patients (Cases 1 and 10) were the tendon reflexes normal.

There was often a similarity between the Holmes-Adie pupils and

those caused by syphilis. Confusion is most likely to arise when the pupils are small, for a delay in constriction and dilatation is naturally more difficult to detect when the range of movement is slight. In all cases, however, the diagnosis of the Holmes-Adie syndrome was firmly established by the clinical findings, and by the negative serological and cerebrospinal fluid reactions.

Investigation of the Pupil in the Holmes-Adie Syndrome

1. The Role of the Sympathetic Innervation in the Holmes-Adie Pupil

HYPOTHESIS (1)

There is no defect of sympathetic innervation in the Holmes-Adie pupil.

PREVIOUS WORK

There are only two records in the literature of the effect of a stellate ganglion block on the Holmes-Adie pupil. Barré and Klein (1934) claimed that this procedure caused enlargement of the pupil and a return to normal speed of the reaction to convergence; there was no change in the reaction to light. Alajouanine and Morax (1938) failed, however, to confirm these results in their patient; there resulted pupillary constriction without any alteration in the reaction to light and convergence.

The effect on the tonic pupil of locally instilled cocaine has been tested more often. Scheie (1940), Sigwald (1941), and Lowenstein and Friedman (1942) reported a normal pupillary dilatation resulting from cocaine, whereas Alajouanine and Morax (1938) thought that the dilatation was exaggerated. Because of his finding, Scheie concluded that the pupillo-dilator mechanism is intact.



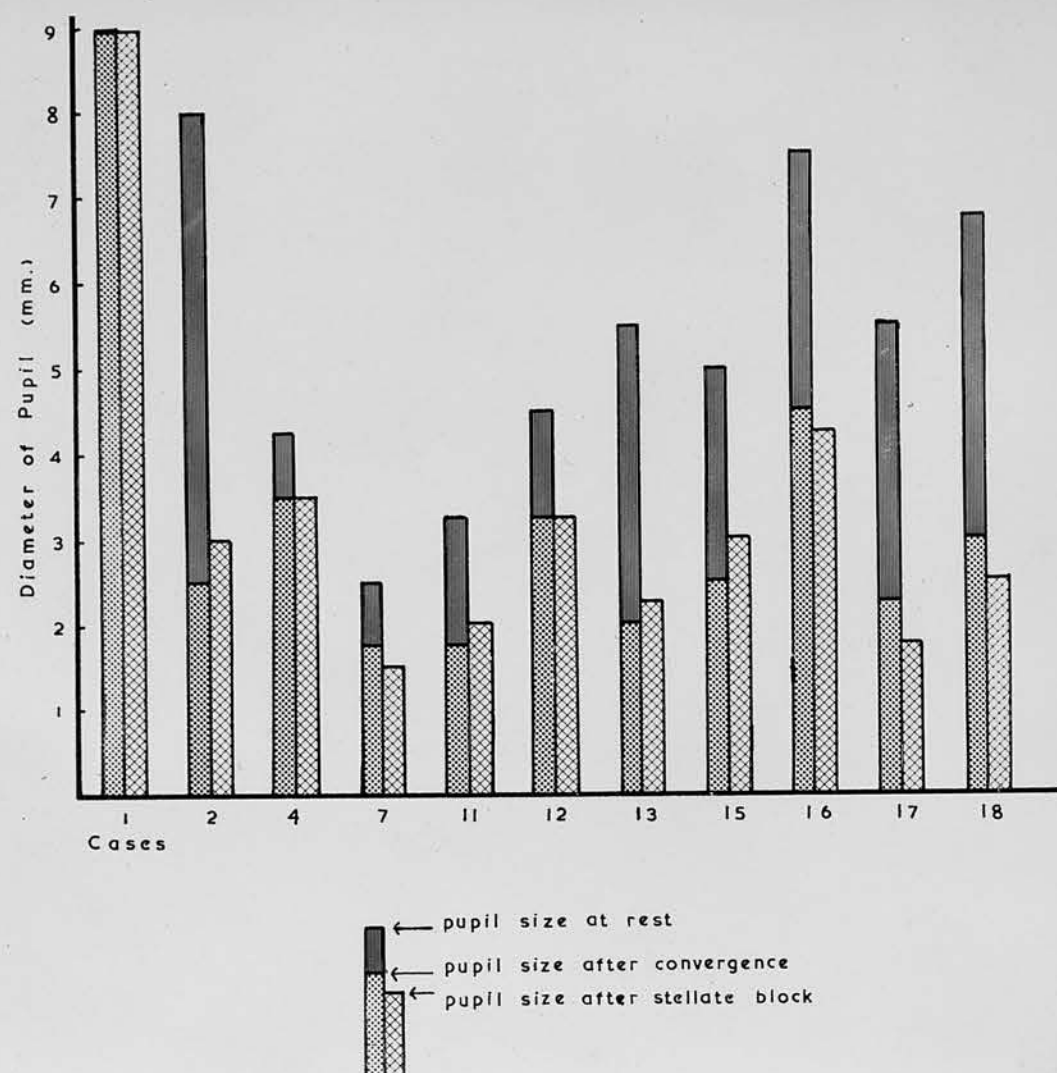


Fig. 8 - Effect of Stellate Ganglion Block on Holmes-Adie Pupils.

In each patient, the size of the pupil reached after stellate ganglion block approximates to that resulting from convergence prior to the block.

TABLE XII

Effect of Sympathetic Block on Holmes-Adie Pupils

CASE	SIDE	PUPIL SIZE (mm.)		
		At rest	After convergence	After sympathetic block
1	L	9	→9	→9
2	L	8	→2½	→3
4	L	4½	→3½	→3½
7	L	2½	→1¾	→1½
11	R	3¼	→1¾	→2
12	R	4½	→3¼	→3¼
13	R	5½	→2	→2½
15	L	5	→2½	→3
16	L	7½	→4½	→4½
17	L	5½	→2½	→1¾
18	R	6¾	→3	→2½

The pupillary constriction resulting from the stellate ganglion block approximates to that caused by convergence.

INVESTIGATIONS

Three investigations were carried out to assess the sympathetic control of the Holmes-Adie pupil.

Investigation 1. - Stellate Ganglion Block

Method. - It was reasoned that if the sympathetic innervation to the abnormal pupil is destroyed, there should result no change from blocking the stellate ganglion. 12 eyes in 11 patients were studied by this method. The pupillary abnormalities of these patients ranged from a completely paralysed pupil in Case 1 to a markedly tonic pupil in Case 2 (left); the other cases showed varying degrees of the tonic reaction. The sympathetic was blocked with procaine as already explained on p. 22. Where the effectiveness of the block could not be gauged by observing the pupil, it was ascertained by the development of ptosis and conjunctival injection. When necessary, facial anhidrosis was also demonstrated by a sweat test (see p. 23). The size of the pupil was measured before and after convergence, and again after the procaine block.

Results. - In the twelve eyes tested, pupillary constriction occurred to a widely varying degree (Table XII and Fig. 8). The fixed dilated pupil of Case 1 was not affected by the block; the tonic pupils responded by a constriction which closely approximated that resulting simply from convergence prior to the block.

Investigation 2. - Conjunctival Instillation of Cocaine Hydrochloride (3%)

Method. - It has already been shown (p. 29) that interference with the sympathetic innervation to the iris can be detected by a loss_

TABLE XIV

Comparison of the Effect of Cocaine on Holmes-Adie and Normal Pupils

CASE	COCAINE 3%	
	Abnormal Pupil (mm.)	Normal or Less Affected Pupil (mm.)
5	$3\frac{1}{4} \rightarrow 4\frac{1}{4}$	$3\frac{1}{2} \rightarrow 4\frac{1}{2}$
6	$3\frac{1}{4} \rightarrow 4\frac{1}{4}$	$5\frac{1}{4} \rightarrow 6\frac{1}{2}$
8	$4\frac{1}{2} \rightarrow 5\frac{1}{2}$	$5\frac{1}{2} \rightarrow 5\frac{3}{4}$
11	$4 \rightarrow 5\frac{1}{2}$	$5\frac{1}{2} \rightarrow 7$

In these patients, the more abnormal pupil was the smaller. Cocaine caused bilateral mydriasis, but the relative size of the two pupils remained unchanged.

TABLE XIII

Effect of Cocaine on Holmes-Adie Pupils

CASE	SIDE	PUPIL AT REST (mm.)	PUPIL AFTER COCAINE (3%) (mm.)
1	L	9	$\rightarrow 9$
2	R L	$5\frac{1}{4}$ $5\frac{3}{4}$	$\rightarrow 7\frac{1}{2}$ $\rightarrow 8\frac{1}{4}$
4	L	$4\frac{1}{4}$	$\rightarrow 5$
5	R L	$3\frac{1}{4}$ $3\frac{3}{4}$	$\rightarrow 4\frac{1}{4}$ $\rightarrow 4\frac{3}{4}$
6	L	$3\frac{1}{4}$	$\rightarrow 4\frac{1}{4}$
7	R L	$2\frac{3}{4}$ $3\frac{1}{4}$	$\rightarrow 3\frac{1}{4}$ $\rightarrow 5$
8	R L	$5\frac{1}{4}$ $4\frac{3}{4}$	$\rightarrow 5\frac{3}{4}$ $\rightarrow 5\frac{1}{2}$
11	R L	4 $5\frac{1}{2}$	$\rightarrow 5\frac{1}{2}$ $\rightarrow 7$
12	R L	5 $4\frac{1}{2}$	$\rightarrow 7\frac{1}{2}$ $\rightarrow 6\frac{1}{2}$
13	L	$5\frac{1}{2}$	$\rightarrow 6\frac{1}{2}$
15	L	$4\frac{1}{2}$	$\rightarrow 7\frac{1}{2}$
16	R L	$3\frac{1}{2}$ 6	$\rightarrow 4\frac{1}{2}$ $\rightarrow 8$
17	R L	$3\frac{1}{4}$ 5	$\rightarrow 5\frac{1}{2}$ $\rightarrow 7$
18	R	6	$\rightarrow 8$
20	L	4	$\rightarrow 4$

The conjunctival instillation of cocaine caused dilatation of the pupil, except in Cases 1 and 20.

partial or complete - of the normal dilatation of the pupil with cocaine. 23 Holmes-Adie pupils were tested. Two drops of cocaine solution were instilled from the same dropper into each eye. In patients with a unilateral Holmes-Adie pupil, it was thus possible to compare the reaction of the affected pupil with that on the normal side. The size of the pupil was measured before the cocaine test and when maximal dilatation had resulted (usually after 20 minutes).

Results. - Table XIII shows that cocaine usually caused a normal mydriatic response. There were two exceptions - Cases 1 and 20. In Case 1, further dilatation of the pupil was not possible. Case 20 was unique in that he was known to have a combined Horner's syndrome and tonic pupil (See appendix, p. 83). Sweating was completely absent from the left half of his face, and the sympathetic lesion was therefore thought to be complete. It was shown on p. 29 that a pupillary dilatation from cocaine is not to be expected in such a case of total sympathetic denervation. It may therefore be said that there was no evidence of a defective sympathetic innervation in the other cases.

Neither was there any evidence of sympathetic over-action, for the cocaine reaction was never greater than normal: when the affected pupil was smaller than its normal or relatively normal fellow, this relation of size remained unaltered (Table XIV).

Investigation 3. - Conjunctival Instillation of Adrenaline Hydrochloride (0.1%)

Method. - Locally instilled adrenaline causes dilatation of the pupil if there is a post-ganglionic interruption of the sympathetic to the iris (Foerster and Gagel, 1932). This reaction

was looked for in 16 abnormal eyes.

Result. - No reaction to adrenaline was found in any of the eyes tested.

DISCUSSION AND CONCLUSIONS

An explanation must be sought for the varying response of the pupils to the stellate ganglion block. Those pupils that were markedly constricted by the procedure must obviously have had an intact sympathetic innervation which maintained a state of dilatation prior to the block. The same pupils were capable of constricting to convergence.

In the case of the pupils that did not respond or responded poorly to the stellate ganglion block, two explanations are suggested. First, it may be that the sympathetic fibres to the iris had been wholly or partly destroyed. The alternative explanation is that the sphincter pupillae could not contract in spite of being released from the intact sympathetic influence. Indeed, it has been shown (p. 26) that when the sphincter pupillae in normal eyes is paralysed by the action of locally instilled homatropine, additional blocking of the sympathetic innervation causes little or no constriction of the dilated pupil. Accordingly, a completely paralysed pupil (as in Case 1) would not be expected to alter.

That the second explanation is the likely one is suggested by the observation that when the abnormal pupil was temporarily released from the influence of the sympathetic innervation, constriction equalled that resulting from convergence. Final proof that the sympathetic control is intact comes from the normal responses to cocaine and adrenaline.

In conclusion, the sympathetic control of the pupil is not defective in the Holmes-Adie syndrome. The preservation of parasympathetic function can be assessed by the reaction to convergence.

HYPOTHESIS (2)

The sympathetic innervation is not responsible for the slow movements of the Holmes-Adie pupil.

PREVIOUS WORK

Barré and Klein (1934) claimed that the speed of constriction of the Holmes-Adie pupil returned to normal after a sympathetic block. This suggests that the sympathetic innervation primarily is responsible for the slow constriction of the pupil. This view was also taken by Garcin and Kipfer (1936) and Lowenstein and Friedman (1942). On the other hand, Alajouanine and Morax (1938) were unable to confirm the observation of Barré and Klein.

INVESTIGATION

If the sympathetic innervation is indeed responsible for the delayed movements of the Holmes-Adie pupil, a stellate ganglion block should restore them to a normal speed.

Methods. - An attempt was made to time the reaction to convergence after the stellate ganglion blocks described in the preceding investigation (p. 52). However, the slowest reacting pupils became the most miotic after the block, so that convergence now caused only a small range of constriction; timing of the response by the naked eye thus became impossible.

Accordingly, a cinephotographic record of the tonic pupil was made before and after the procaine block (see p. 22). The left pupil

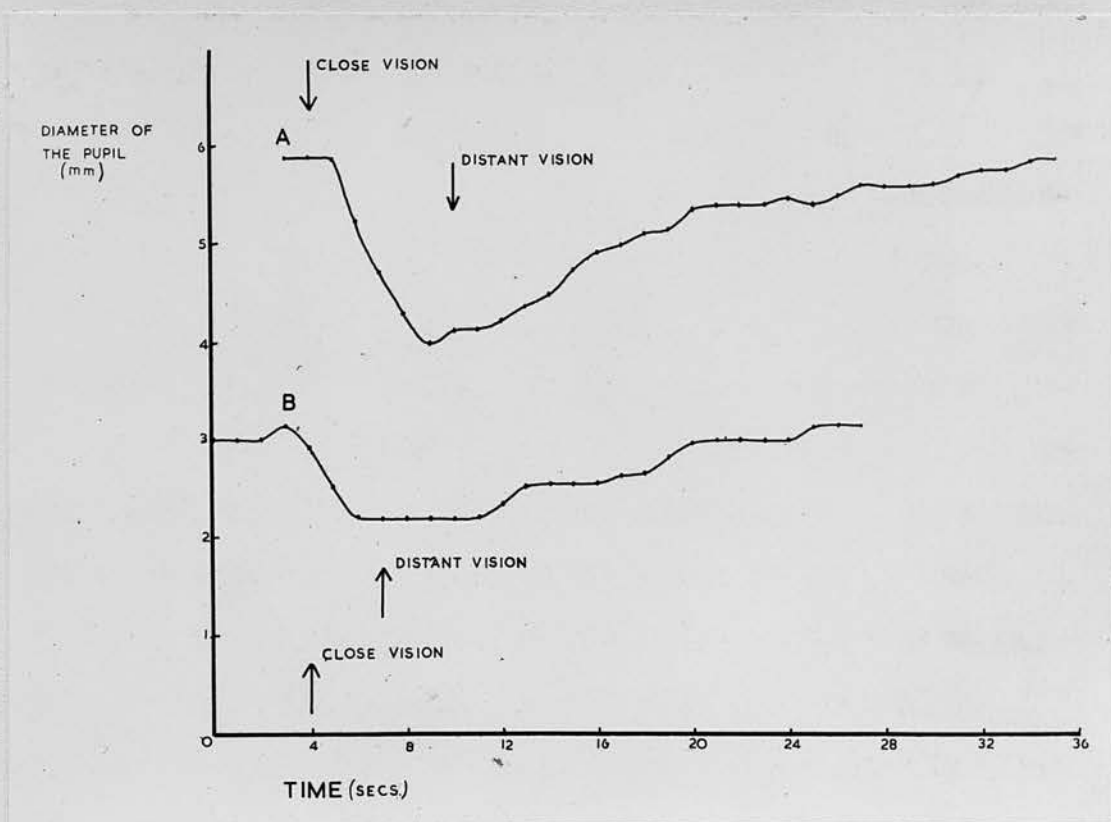


Fig. 9 - Effect of Stellate Ganglion Block on the Tonic Reaction of the Pupil.

- A. Response of the tonic pupil before stellate ganglion block - there is a delay of 23 sec. before the pupil returns to its original size after relaxation of convergence.
- B. Response of the tonic pupil after stellate ganglion block - the rate of dilatation remains unaltered.

of Case 2 was chosen because its response to convergence was extremely slow. Particular attention was paid to the phase of pupillary dilatation, always much slower than that of constriction. Fig. 1 shows representative exposures at four-second intervals before and after the block.

Results. - Fig. 9 is a pupillographic record of the response of this pupil to convergence before (A) and after (B) the stellate ganglion block. Tracing (B) shows not only that the resting pupil was smaller as a result of the block, but that the range of constriction in response to accommodation was diminished (from 1.9 mm. to 0.9 mm.). When accommodation was relaxed, the time taken for the return of the pupil to its resting size was 23 seconds before the block and 13 seconds after the block. When these time intervals are equated with the reduced range of movement, it is seen that there was no alteration in the speed of pupillary relaxation. The comparable slopes of the two curves in Fig. 9 provide further confirmation that the slow movements of the Holmes-Adie pupil are not dependent on an intact sympathetic innervation.

DISCUSSION AND CONCLUSIONS

A sympathetic block superimposes an Horner's syndrome on the tonic pupil. The pupil becomes smaller and its reaction to convergence is reduced in range, but its speed remains unaltered. These findings are in keeping with the formulated hypothesis that the slow movements of the pupil cannot be mediated by the sympathetic innervation. Thus, the observation of Alajouanine and Morax (1938) is substantiated and that of Barré and Klein is refuted.

ii. The Sensitivity of the Holmes-Adie Pupil to Parasympathomimetic Drugs

HYPOTHESIS

The sensitivity of the Holmes-Adie pupil to parasympathomimetic drugs varies directly with its tonic reaction.

DEFINITION

It was seen on p. 11 that the term "tonic reaction" covers two characteristics: the slowness of movement of the pupil and its preserved range of constriction in response to convergence.

PREVIOUS WORK

The parasympathomimetic drugs studied have included acetyl B methyl choline ("Mechoyl"), eserine and pilocarpine. In 1940, Adler and Scheie showed that the tonic pupil was constricted by a $2\frac{1}{2}\%$ solution of acetyl B methyl choline, instilled into the conjunctival sac; the same concentration had no effect on the normal pupil. There have since been reports confirming the value of this test, especially in distinguishing the tonic from the syphilitic pupil. (Sykowski, 1951; Sproffkin, 1953). Graveson (1949) and Henberger (1954), however, obtained this response in only less than half the pupils they studied. A note of caution was sounded by Brunnenschweiler (1954), who described a constriction with the drug in some of his normal controls, but nevertheless accepted its diagnostic value when a strongly miotic reaction occurred.

Most workers who observed the effect of local eserine and pilocarpine on the tonic pupil reported that these drugs caused normal constriction (Markus, 1906; Holmes, 1931; Heersema and Moersch, 1939; Scheie, 1940; James, 1944; Duke-Elder, 1949). Only

Alajouanine and Morax (1938) described a precocious and exaggerated miosis with either eserine or pilocarpine. Lowenstein and Friedman (1942) claimed that eserine momentarily restored the reaction to light, a finding which Graveson (1949) was unable to verify.

INVESTIGATIONS

The following parasympathomimetic drugs were tested:-

1. Acetyl B methyl choline, 2½% ("Mecholyl" - Savory and Moore) - in 24 Holmes-Adie pupils.
2. Eserine sulphate, 0.25% - in 17 Holmes-Adie pupils.
3. Pilocarpine nitrate, 1% - in 21 Holmes-Adie pupils.

These drugs were used rather than acetylcholine because of their greater stability and convenience. When used in the given concentrations, they have the following effect on the normal eye: eserine produces a maximal pupillary constriction, pilocarpine causes a moderate constriction and Mecholyl is without any effect.

Method. - Two drops of the chosen solution were instilled into the conjunctival sacs of both eyes. By this means, the reaction of the two pupils in the same patient could be compared; this was of value when one of the pupils was normal. The maximal constriction produced by the drug was reached within 20 to 40 minutes, and was compared with the original size of the pupil.

The response to pilocarpine was chosen to represent the sensitivity of each Holmes-Adie pupil to this group of substances. The patients with the Holmes-Adie syndrome were examined in different hospitals under varying conditions of illumination. In order to allow comparison between the pupils, and bearing in mind the uncontrolled lighting conditions, 21 Holmes-Adie pupils among 19

TABLE XVI

Comparison of the Effect of Eserine on Holmes-Adie and Normal Pupils

CASE	ESERINE $\frac{1}{4}\%$	
	Abnormal Pupil (mm.)	Normal or Less Affected Pupil (mm.)
2	$7\frac{1}{2} \rightarrow 1\frac{1}{2}$	$3 \rightarrow 1\frac{3}{4}$
7	$3\frac{1}{4} \rightarrow 1$	$3 \rightarrow 1\frac{3}{4}$
13	$4\frac{1}{2} \rightarrow 1\frac{3}{4}$	$4\frac{1}{4} \rightarrow 2$
16	$6 \rightarrow 1\frac{1}{4}$	$3\frac{1}{2} \rightarrow 1\frac{1}{2}$

Increased sensitivity of the Holmes-Adie pupil to eserine is shown by a more marked constriction of the abnormal pupil which was originally larger than the normal pupil.

TABLE XV

Effect of Acetyl B Methyl Choline (2.5%) on Holmes-Adie Pupils

CASE	SIDE	PUPIL AT REST (mm.)	PUPIL AFTER "MECHOLYL" (mm.)
1	L	9	$\rightarrow 9$
2	R L	$5\frac{1}{8}$ $6\frac{3}{4}$	$\rightarrow 5$ $\rightarrow 4\frac{1}{4}$
4	L	$4\frac{1}{4}$	$\rightarrow 3\frac{1}{4}$
6	L	$3\frac{1}{4}$	$\rightarrow 2\frac{3}{4}$
7	R L	$2\frac{3}{4}$ $3\frac{1}{4}$	$\rightarrow 2\frac{3}{4}$ $\rightarrow 1\frac{1}{2}$
8	R L	$4\frac{1}{4}$ 4	$\rightarrow 4\frac{1}{4}$ $\rightarrow 4$
9	R L	$4\frac{1}{4}$ $6\frac{1}{2}$	$\rightarrow 4\frac{1}{4}$ $\rightarrow 5\frac{1}{4}$
11	R L	4 $5\frac{1}{2}$	$\rightarrow 4$ $\rightarrow 4\frac{1}{4}$
12	R L	5 5	$\rightarrow 4$ $\rightarrow 5$
13	R	5	$\rightarrow 4$
16	R L	$4\frac{1}{2}$ $6\frac{1}{2}$	$\rightarrow 2\frac{1}{4}$ $\rightarrow 4\frac{1}{2}$
17	R L	$3\frac{1}{4}$ $4\frac{1}{2}$	$\rightarrow 2\frac{3}{4}$ $\rightarrow 2\frac{1}{2}$
18	R	$6\frac{3}{4}$	$\rightarrow 4\frac{1}{2}$
19	R L	$8\frac{1}{4}$ $6\frac{1}{4}$	$\rightarrow 8\frac{1}{4}$ $\rightarrow 6\frac{1}{4}$
20	L	4	$\rightarrow 4$

"Mecholyl" caused a varying constriction of the pupil in 14 out of the 24 pupils tested.

patients were selected in which the reaction to light was lost or very much impaired. The sensitivity to pilocarpine was measured by the arithmetic difference between the diameters (in mm.) of the pupil at rest and after maximal constriction by the drug. The difference obtained was correlated with the tonicity of the pupil, which, it has already been said, includes:-

- a. the response of the pupil to convergence and
- b. the time delay before it returns to its original size after relaxing convergence.

The response to convergence was measured (in mm.) by subtracting the diameter of the pupil after maximal constriction from that of the pupil at rest. The delay in dilatation of the pupil was timed (in seconds) with a stopwatch, the mean of six readings being taken.

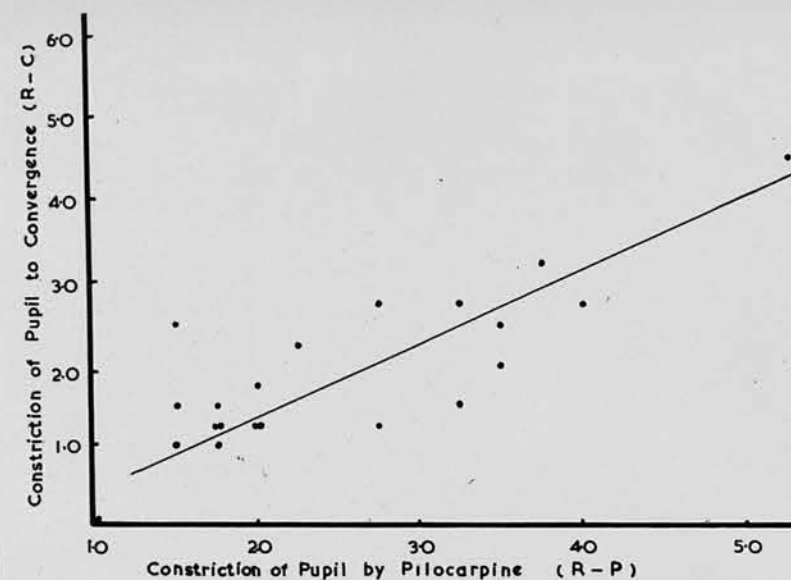
Results. - The three parasympathomimetic drugs had the same relative effect on the Holmes-Adie as on the normal pupil, but the resulting miosis varied from case to case.

1. "Mechoyl" ($2\frac{1}{2}\%$). - The responses of 24 Holmes-Adie pupils are shown in Table XV. No effect was seen in ten eyes. In 7 eyes a pupillary constriction of 1 mm. or less was noted, and in the remaining 7 eyes the constriction was greater than 1 mm.

2. Eserine ($\frac{1}{4}\%$). - A clear-cut increase in sensitivity to eserine was found in 4 of the 11 patients tested (Table XVI). The abnormal pupil, which was the larger before the test, became the smaller during the period of maximal influence of the drug. Furthermore, the constriction of the abnormal pupil was frequently more prolonged by several hours than that of the normal pupil.

3. Pilocarpine (1%). - The results of examining 21 pupils in

A



B

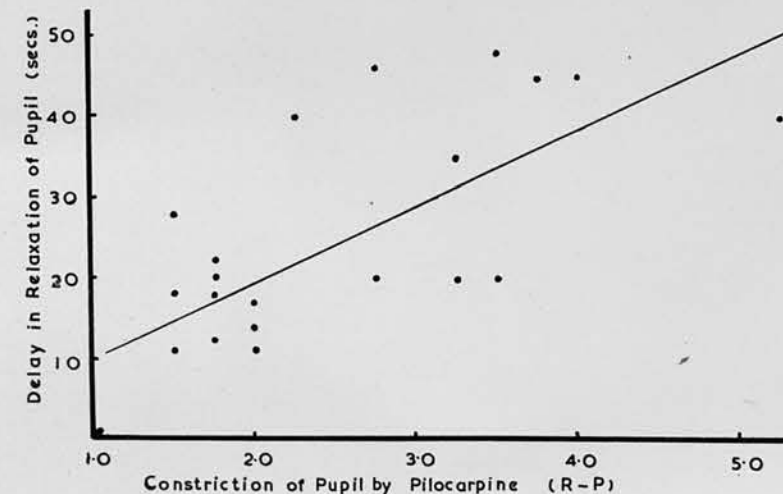


Fig. 10 - Sensitivity of the Holmes-Adie Pupil to Pilocarpine.

- A. There is an approximate linear relationship between the sensitivity of the Holmes-Adie pupil to instilled pilocarpine and the reaction to convergence.
- B. There is also a linear relationship between the sensitivity of the Holmes-Adie pupil to pilocarpine and the delay in pupillary relaxation.

TABLE XVIII

Effect of Pilocarpine (1%) on Holmes-Adie Pupils - Analysed Data

CASE	SIDE	(x) R - P	(y) R - C	(z) Time
1	L	1.00	0	0
2	R	1.50	1.00	11
	L	5.25	4.50	40
3	R	1.50	2.50	18
4	L	1.75	1.25	12
5	R	1.75	1.00	18
6	L	1.75	1.25	22
7	L	1.75	1.50	20
8	L	2.00	1.25	11
9	R	2.00	1.25	14
10	L	2.00	1.75	17
11	R	2.25	2.25	40
12	R	2.75	1.25	20
13	R	2.75	2.75	46
14	L	3.25	1.50	35
15	L	3.25	2.75	20
16	L	3.50	2.00	20
17	R	1.50	1.50	28
	L	3.50	2.50	48
18	R	3.75	3.25	45
19	L	4.00	2.75	45

1. R-P is the constriction caused by pilocarpine (size of pupil at rest - size of pupil when fully constricted by pilocarpine).
2. R-C is the constriction due to convergence (size of pupil at rest - size of pupil after convergence).
3. Time is the interval in seconds required for pupillary dilatation.

Coefficients of correlation between x and y, and x and z were calculated:-

$$\begin{array}{lll} r_{xy} = +.82 & d.f. = 19 & P = < .001 \\ r_{xz} = +.71 & d.f. = 19 & P = < .001 \end{array}$$

TABLE XVII

Effect of Pilocarpine (1%) on Holmes-Adie Pupils - Raw Data

CASE	SIDE	PUPIL AT REST (mm.)	PUPIL AFTER CONVERGENCE (mm.)	PUPIL AFTER PILOCARPINE 1% (mm.)	TIME FOR RELAXATION OF PUPIL (secs.)
1	L	9	→ 9	→ 8	0
2	R	5½	→ 4½	→ 3½	11
	L	7½	→ 3	→ 2½	40
3	R	4¾	→ 2¼	→ 3¼	18
4	L	4½	→ 3¼	→ 2¾	12
5	R	3¾	→ 2¾	→ 2	18
6	L	3½	→ 2¼	→ 1¾	22
7	L	3¼	→ 1¾	→ 1½	20
8	L	4	→ 2¾	→ 2	11
9	R	4¼	→ 3	→ 2¼	14
10	L	5¼	→ 3½	→ 3¼	17
11	R	4	→ 1¾	→ 1¾	40
12	R	4½	→ 3¼	→ 1¾	20
13	R	4½	→ 1¾	→ 1¾	46
14	L	5	→ 3½	→ 1¾	35
15	L	5½	→ 2¾	→ 2¼	20
16	L	6½	→ 4½	→ 3	20
17	R	3¼	→ 1¾	→ 1¾	28
	L	5¼	→ 2¾	→ 1¾	48
18	R	7	→ 3¾	→ 3¼	45
19	L	6¼	→ 3½	→ 2¼	45

The pupillary constriction resulting from pilocarpine is compared with that caused by convergence, and with the time required for relaxation of the pupil after convergence.

19 patients are shown in Table XVII. A correlation was sought between on the one hand, the response of the abnormal pupil to pilocarpine, and on the other, the response to convergence and the time delay for subsequent dilatation. The analysed data are given in Table XVIII. The coefficient of correlation between the reaction to pilocarpine and the reaction to convergence was + .82. The coefficient of correlation between the reaction to pilocarpine and the time delay was + .71.

This signifies that there is a direct relationship between the sensitivity of a pupil to pilocarpine and its response to convergence, and a less marked but still highly significant relationship between the sensitivity to pilocarpine and the time delay. These linear relationships are illustrated in Fig. 10.

One patient (Case 2, right) was repeatedly tested with pilocarpine after developing an internal ophthalmoplegia in October 1955. She was tested two days after the onset of symptoms when the pupil constricted only from $5\frac{1}{2}$ to $3\frac{1}{2}$ mm. Two months later, the pupil had become much more sensitive to pilocarpine, constricting to $1\frac{3}{4}$ mm.; it remained fixed, however, until March 1956, when there was a slight return of the reaction to convergence, which was delayed (dilatation took 10 seconds). When the patient was seen again in December 1956, there was a frankly tonic reaction; the response to convergence amounted to $3\frac{1}{2}$ mm. and the subsequent dilatation took 50 seconds. Thus, the sensitivity to pilocarpine had preceded the tonic reaction by about three months.

DISCUSSION AND CONCLUSIONS

More than half the Holmes-Adie pupils tested showed some

constriction after instilling a $2\frac{1}{2}\%$ solution of acetyl B methyl choline. The response was taken as significant only in the seven abnormal pupils in which a decrease in diameter of more than 1 mm. was observed, for Brunnschweiler has stated that normal pupils may react slightly to the drug.

There was also an increased sensitivity of some tonic pupils to eserine and pilocarpine as shown by a miosis which was both more marked and more prolonged than in the normal eye. The degree of this sensitivity varied from one abnormal pupil to another. The effect of pilocarpine was quantified and found to depend on those two characteristics which determine the tonicity of the pupil - its range of movement induced by convergence and the delay for its subsequent dilatation. In one case, the sensitivity to pilocarpine preceded the clinical manifestations of tonicity by about three months. These findings are in agreement with the formulated hypothesis. Support is also given to the observation of Alajouanine and Morax that tonic pupils may be hypersensitive to parasympathomimetic drugs.

iii. Investigation of Accommodation in the Holmes-Adie Syndrome

HYPOTHESIS

In the later stage of the Holmes-Adie syndrome the ciliary muscle regains the power of contraction, and becomes slow in its movements and hypersensitive to the action of parasympathomimetic drugs. In other words, accommodation undergoes changes similar to those of the pupil and becomes tonic in its response.

PREVIOUS WORK

There is only inadequate reference in the literature to the disturbance of accommodation in the Holmes-Adie syndrome. Some authors have mentioned the initial paralysis of accommodation which is followed by delayed accommodation or by recovery (Holmes, 1931; Van Leeuwen, 1946; Graveson, 1949). The lack of information on this subject may stem from the inaccuracy of the methods hitherto employed. Some of the possible methods of investigating accommodation will now be reviewed.

(1) Measurement of Accommodation. - The range of accommodation has usually been assessed by measuring the near point without any reference to the patient's refractive error (Graveson, 1949). This method has the additional disadvantage of relying entirely on the patient's estimate of the near point.

(2) The Delay of Accommodation. - Only Graveson attempted a systematic investigation of the delay involved when the patient looked from a distant object to a close one, and vice versa. For the close object, he used a Jaeger test-card which could be read comfortably at a distance greater than the near point (usually J4 to J8). He timed with a stopwatch the delay before the near or distant object became sharply focused, and found it abnormally long in 16 out of 22 eyes examined. In the majority of cases this time-lag occurred only during accommodation from far to near vision. This method cannot be considered entirely satisfactory because the speed of accommodation has been shown to depend on the size of the test object (Umetani, 1954).

(3) The response of accommodation to parasympathomimetic drugs. -

There have been no studies analogous to those of acetyl B methyl choline and other parasympathomimetic drugs on the pupil.

INVESTIGATIONS

Attempts were made to measure the range of accommodation, its speed, and the effect of pilocarpine on the ciliary muscle.

Subjects Examined

Accommodation was measured in 15 patients with the Holmes-Adie syndrome. Table XIX gives details of their age, sex and ocular refraction. Among these patients 20 eyes were selected for examination, using two criteria:-

a. Each eye had to show a well established tonic pupil. The severity of the pupillary abnormality was judged by the abolition or severe impairment of the light reflex.

b. A sufficient interval of time had to elapse after the onset of the disorder (14 months or longer). This interval would permit the development of tonic accommodation if such a change was going to occur.

It was considered essential to compare the eyes of the Holmes-Adie patients with the eyes of normal subjects, and to match each patient with a normal subject for age and sex. It is well known that normal accommodation diminishes with age. Owing mainly to sclerotic changes in the crystalline lens, accommodation decreases from birth onwards, until it is lost around the age of fifty to sixty; different ages are quoted for the total loss of accommodation, according to the authority and method of measurement (Hamasaki et al, 1956). Furthermore, for any given age, there is a physiological

TABLE XX

Range of Accommodation in the Holmes-Adie Syndrome

CASE	SIDE	RANGE OF ACCOMMODATION (DIOPTRES)		
		(a) Holmes-Adie	(b) Normal	(c) Difference Between (a) & (b)
4	L	0	0	0
12	R	0	0	0
	L	0	0	0
20	L	0	0	0
18	R	0	0.3	- 0.3
10	L	1.1	3.1	- 2.0
9	R	1.0	2.5	- 1.5
11	R	5.1	1.5	+ 3.6
	L	3.3	2.0	+ 1.3
6	L	2.8	1.5	+ 1.3
17	R	5.1	6.7	- 1.6
	L	2.2	6.5	- 4.3
3	R	4.6	5.3	- 0.7
15	L	5.2	4.2	+ 1.0
8	L	2.3	5.4	- 3.1
2	R	6.2	8.7	- 2.5
	L	7.2	9.1	- 1.9
16	L	5.1	7.7	- 2.6

Column (c) gives the differences between the range of accommodation in the Holmes-Adie patients and the normal controls (a negative sign shows that accommodation is less in the patient). The means between the two groups were compared by a t-test (for correlated means).

$$t = 1.66$$

$$d.f. = 17$$

$$P = > .05$$

TABLE XIX

Data of Holmes-Adie Patients and Matched Normal Subjects

HOLMES-ADIE PATIENTS					NORMAL CONTROLS				
Case	Age	Sex	Side	Refraction	Case	Age	Sex	Side	Refraction
4	57	F	L	+ 0.9	1	57	F	L	+ 1.4
12	56	F	R	+ 3.8	2	56	F	R	+ 1.2
			L	+ 3.2				L	+ 1.2
20	53	M	L	- 0.1	3	53	M	L	- 1.2
18	49	M	R	+ 0.7	4	48	M	R	+ 1.5
10	43	M	L	+ 0.7	5	43	M	L	+ 2.4
9	42	M	R	- 1.4	6	41	M	R	+ 2.3
11	38	F	R	+ 0.3	7	38	F	R	- 0.5
			L	0.0				L	+ 0.1
6	38	F	L	+ 1.1	8	38	F	L	- 0.3
17	37	F	R	0.0	9	37	F	R	- 0.1
			L	+ 1.3				L	+ 0.1
3	37	F	R	+ 0.2	10	37	F	R	- 1.7
15	36	M	L	- 2.7	11	37	M	L	+ 0.3
8	35	F	L	+ 3.9	12	35	F	L	+ 0.6
2	26	F	R	+ 0.5	13	26	F	R	- 0.7
			L	+ 0.7				L	- 0.8
19	22	M	R	- 0.3	14	21	M	R	- 0.2
			L	- 2.8				L	- 0.3
16	21	F	L	- 0.4	15	21	F	L	+ 0.3

The patients and normal controls were matched for age, sex and eye tested. Gross refractive errors were avoided in the control group.

range of up to four dioptries for normal accommodation (Duane, 1925). A particular effort was made to obtain a close agreement in age; the age in years of the normal control agreed exactly with that of the patient in 11 cases, and within a year in 4 cases (Table XIX). Care was also taken not to include as a normal control any subject with a severe refractive error. Where the abnormality was bilateral, both eyes of the control were tested: where it was unilateral, only the corresponding eye was examined.

Investigation 1. - Measurement of the Range of Accommodation

Method. - Refraction and accommodation were measured with Fincham's coincidence optometer (see p. 24). A high degree of accuracy was attained with this instrument. The range of accommodation was determined by the difference between the refraction of the eye when relaxed and when fully accommodated for near vision. Values for 18 eyes among 14 Holmes-Adie patients were compared with 18 normal eyes, in order to decide if accommodation was significantly reduced in the Holmes-Adie group. One patient (Case 19) had an amblyopic left eye and the coincidence optometer did not provide an adequate stimulus to accommodation, so that no readings were obtained.

Results. - Table XX shows how the range of accommodation in the Holmes-Adie patients (column 1) differed from that in the normal controls (column 2). The differences between the two groups are shown in column 3; a negative sign indicates that accommodation was less in the abnormal eye. The means between the abnormal and control groups were compared by a t-test (for correlated means). The range of accommodation for the Holmes-Adie group was found to be slightly reduced in comparison with that of the normal group, but this

TABLE XXI

Delay in Accommodation for Near Vision

CASE	SIDE	DELAY IN ACCOMMODATION FOR NEAR VISION (Secs.)
1	L	13
2	R L	10 5
3	R	3
6	L	< 2
8	L	7
9	R L	6 3
10	R L	7 6
11	R L	8 13
15	L	3
16	L	< 2
17	R L	4 < 2
19	L	3

A delay of less than two seconds was considered normal.

Accommodation was abnormally delayed in 14 out of 17 abnormal eyes tested.

difference was found to be not significant ($P = > .05$).

Investigation 2. - The Delay of Accommodation

Methods. - It was not possible to time accommodation with the coincidence optometer, for even normal subjects sometimes failed to respond for several seconds to the stimulus of rapidly altering vergence of light. The delay in accommodating for near or distant vision was also influenced by practice and by instruction, so that consistent observations were not obtainable.

Graveson's clinical method was therefore used for measuring the delay in accommodation for near vision in the Holmes-Adie patients (see p. 62). The limitations of the method have already been pointed out and no important conclusions will be drawn from the results. Estimations were restricted to 10 patients under the age of 45, because presbyopic changes in older patients made timing inaccurate. Among these patients, 17 eyes with tonic pupils were examined.

Results. - Accommodation for near vision was found to be delayed in 14 out of the 17 eyes examined. The time lag varied from 3 to 13 seconds (Table XXI).

Investigation 3. - The Response of Accommodation to Pilocarpine

Method. - Accommodation was measured with the coincidence optometer. Two drops of 1% pilocarpine nitrate were then instilled from a pipette into the eye, which was later re-examined at five-minute intervals until the maximum effect of the drug was observed. This usually took from 20 to 30 minutes.

Fig. 11 shows the effect of this test on a normal subject; for any given strength of accommodative stimulus, there tended to be an enhanced accommodative response after the administration of pilo-

TABLE XXII

Action of Pilocarpine on Accommodation in the Holmes-Adie Syndrome

CASE	SIDE	SPASM OF ACCOMMODATION (DIOPTRES)		
		(a) Holmes-Adie	(b) Normal	(c) Difference between (a) & (b)
4	L	0.7	0	+ 0.7
12	R	1.2	0	+ 1.2
	L	0.4	0	+ 0.4
20	L	0	0	0
18	R	2.0	0.5	+ 1.5
10	L	1.2	0.1	+ 1.1
9	R	0.4	0	+ 0.4
11	R	2.6	1.0	+ 1.6
	L	2.0	1.7	+ 0.3
6	L	2.5	0.6	+ 1.9
17	R	0.8	1.8	- 1.0
	L	1.0	1.1	- 0.1
3	R	0.1	3.1	- 3.0
15	L	4.3	0.5	+ 3.8
8	L	0.3	0.3	0
2	R	4.2	0.7	+ 3.5
	L	0.3	1.0	- 0.7
19	R	5.5	1.4	+ 4.1
	L	4.8	2.8	+ 2.0
16	L	0.6	0	+ 0.6

Column (c) gives the differences between the spasm of accommodation due to pilocarpine in the Holmes-Adie patients and the normal controls (a positive sign shows that the spasm is greater in the patient). The means between the two groups were compared by a t-test (for correlated means).

$$t = 2.42$$

$$d.f. = 19$$

$$P = < .05$$

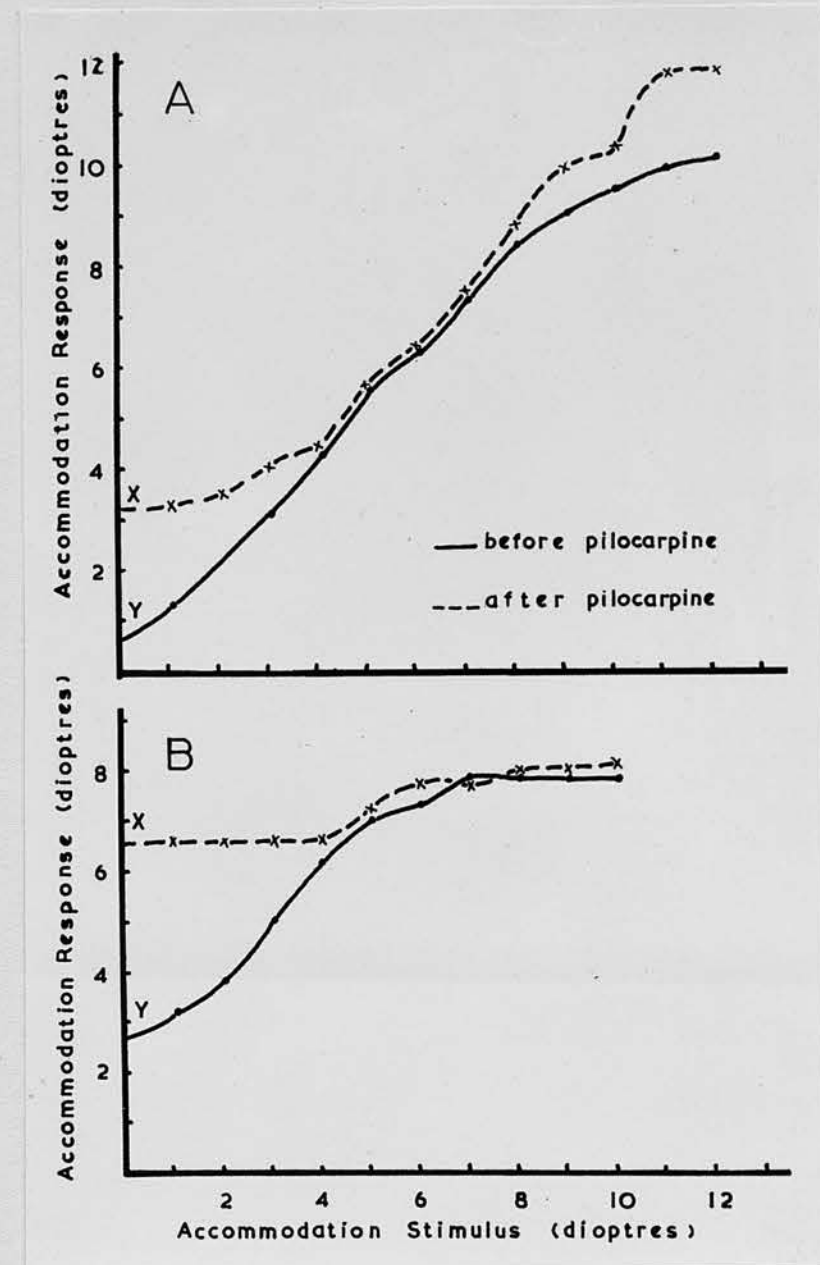


Fig. 11 - Effect of Instillation of Pilocarpine Nitrate (1%) on Accommodation.

After pilocarpine, the subject is unable to relax accommodation fully. Spasm of accommodation is represented by distance XY which is greater in the patient with Holmes-Adie Syndrome (B) than in the normal subject (A).

carpine. This is in agreement with the findings of Finoham (1955), who used eserine instead of pilocarpine. Another feature of the reaction to pilocarpine was an inability of the ciliary muscle to relax fully, as shown by a more "myopic" reading (X instead of Y in Fig. 11) when the accommodative stimulus was withdrawn. This inability to relax accommodation, or spasm of accommodation, was chosen as a measure of the effect of pilocarpine on the ciliary muscle, and is represented in Fig. 11 by the distance XY (expressed in dioptries).

The effect of pilocarpine was tested in 20 eyes with tonic pupils among 15 Holmes-Adie patients. The induced spasm of accommodation was determined in each abnormal eye and compared with:-

- a. The spasm of accommodation in the normal control eye.
- b. The response to pilocarpine of the tonic pupil of the same eye. It was shown on p. 59 that this response of the pupil could be measured by the arithmetic difference between the pupillary diameters (in mm.) before and after treatment with the drug. A new set of measurements of the pupil was obtained at the same time as accommodation was tested.

Results. - a. Table XXII shows how the accommodation of Holmes-Adie patients differed in its response to pilocarpine from that of normal subjects: a positive sign indicates that the spasm of accommodation was greater in the abnormal eye. The means between the Holmes-Adie and control groups were compared by a t-test (for correlated means). The spasm of accommodation for the Holmes-Adie group was found to be significantly increased in comparison with the normal group ($P = < .05$).

- b. A correlation was sought between the effect of pilocarpine

TABLE XXIII

Comparison of the Action of Pilocarpine on the Pupil and
on Accommodation

CASE	SIDE	SIZE OF PUPIL (mm.)			REFRACTION (DIOPTRES)		
		(a) Before Pilocarpine	(b) After Pilocarpine	(c) R - P	(d) Before Pilocarpine	(e) After Pilocarpine	(f) Spasm of Accommod.
4	L	5	2 $\frac{1}{4}$	2.75	+ 0.9	+ 0.2	0.7
12	R	5 $\frac{3}{4}$	1 $\frac{3}{4}$	4.00	+ 3.8	+ 2.6	1.2
	L	5 $\frac{1}{2}$	1 $\frac{3}{4}$	3.50	+ 3.2	+ 2.8	0.4
18	R	7 $\frac{1}{4}$	2 $\frac{3}{4}$	4.50	+ 0.7	- 1.3	2.0
10	L	5 $\frac{1}{2}$	3 $\frac{1}{4}$	2.00	+ 0.7	- 0.5	1.2
9	R	4 $\frac{1}{2}$	2 $\frac{1}{4}$	2.00	- 1.4	- 1.8	0.4
11	R	4 $\frac{1}{4}$	2 $\frac{1}{4}$	2.00	+ 0.3	- 2.3	2.6
	L	5 $\frac{1}{2}$	2 $\frac{1}{2}$	3.00	0	- 2.0	2.0
6	L	4	1 $\frac{3}{4}$	2.25	+ 1.1	- 1.4	2.5
17	R	3 $\frac{1}{4}$	1 $\frac{3}{4}$	1.50	0	- 0.8	0.8
	L	4 $\frac{1}{2}$	1 $\frac{3}{4}$	2.75	+ 1.3	+ 0.3	1.0
3	R	4 $\frac{3}{4}$	3 $\frac{1}{4}$	1.50	+ 0.2	+ 0.1	0.1
15	L	5 $\frac{3}{4}$	2 $\frac{1}{4}$	3.50	- 2.7	- 7.0	4.3
8	L	4 $\frac{1}{2}$	3 $\frac{1}{4}$	1.00	+ 3.9	+ 3.6	0.3
2	R	5 $\frac{1}{2}$	1 $\frac{3}{4}$	3.50	+ 0.5	- 3.7	4.2
	L	7	3 $\frac{1}{2}$	3.50	+ 0.7	+ 0.4	0.3
19	R	7 $\frac{3}{4}$	2 $\frac{1}{4}$	5.50	- 0.3	- 5.8	5.5
	L	6 $\frac{1}{4}$	2 $\frac{1}{4}$	4.00	- 2.8	- 7.6	4.8
16	L	5 $\frac{3}{4}$	3 $\frac{1}{4}$	2.50	- 0.4	- 1.0	0.6

Column (c) is the pupillary constriction caused by pilocarpine (a-b).

Column (f) is the spasm of accommodation caused by pilocarpine (d-e).

The coefficient of correlation between (c) and (f) was calculated:-
r of = + .59 d.f. = 17 P = < .01

on accommodation and on the size of the tonic pupil of the same abnormal eye (See Table XXIII). A correlation coefficient of + .59, significant at the 1% level, was obtained. This indicates that the sensitivity of the ciliary muscle to pilocarpine tends to increase with that of the sphincter pupillae in the Holmes-Adie syndrome.

DISCUSSION AND CONCLUSIONS

Fifteen patients with tonic pupils of long-standing were examined for remaining signs of abnormal accommodation. It was confirmed that a considerable recovery takes place in the range of accommodation; in fact no significant difference could be detected between the Holmes-Adie group and the normal controls. In many patients, a delay of accommodation develops, which is the defect most easily detected by clinical methods. The group of Holmes-Adie eyes showed a significant increase in sensitivity of the ciliary muscle to pilocarpine.

The disturbance of accommodation therefore undergoes a series of changes strictly analogous to those of the tonic pupil: the ciliary muscle eventually recovers its ability to contract and the movement of contraction becomes slower. The ciliary muscle also develops a heightened sensitivity to pilocarpine. Furthermore, this increase in sensitivity bears some relationship to that of the iris. It may therefore be deduced that the pathological processes affecting accommodation and the pupil are very similar, if not identical.

CHAPTER VII

GENERAL DISCUSSION

The theoretical implications of the preceding observations and the remaining problems will now be discussed.

THE SYPHILITIC PUPIL

THE MIOSIS

The present investigation was confined to determining whether or not a sympathetic lesion is responsible for the miosis in syphilis, as originally suggested by Argyll Robertson (1869) and later accepted by Marina (1901), Dupuy-Dutemps (1905), Wilson (1921), and Merritt and Moore (1933). This explanation was refuted as it was shown that a large syphilitic pupil could not be converted into a truly miotic one simply by blocking the sympathetic innervation of the iris. Moreover, there was often evidence in the miotic syphilitic pupils of the preservation of at least some sympathetic function.

To explain the miosis, we may therefore reconsider the theories of parasympathetic overaction (Behr, 1925; Lowenstein, 1956), and of structural changes of the iris (McGrath, 1932; Apter, 1954). All the evidence points against a parasympathetic overaction causing the miotic pupil because it should then be readily susceptible to the action of atropine.

Before accepting the presence of structural changes in the iris as responsible for the constricted pupil, other possibilities should be considered. The observations of Nash and Woodbury (1953) are of some interest in this connection. They described the occurrence in dogs of a tight pupillary constriction resulting from puncturing the

cornea with a fine needle; atropine failed to dilate the pupil. These workers suggested that the miosis was due to an axon reflex originating from the cornea. Recently, Ambache (1957) followed the lead given by the observation that atropine-resistant miosis results from stimulation of the iris or fifth cranial nerve. He isolated a new pharmacologically active substance, irin, from the rabbit's iris. Irin is distinct from acetylcholine and causes a constriction of the pupil, which is resistant to the action of atropine. 5-hydroxy-tryptamine is another physiologically-occurring substance which has been shown to produce constriction of the pupil in the cat (Page, 1952).

There may be, therefore, substances distinct from the acetylcholine-cholinesterase system which are capable of influencing pupil size in health and disease. These substances, and irin in particular, may play a role in the atropine-resistant miosis of the syphilitic pupil.

THE PTOSIS

The theory that a sympathetic lesion may cause the ptosis which frequently accompanies the abnormal pupil of syphilis, was rejected because of the observed effect of stellate ganglion blocks. Little attention has been paid to the mechanism of the bilateral ptosis which imparts the characteristic facial appearance to the tabetic patient. Only Ingvar (1928) proposed an alternative explanation - that the nerve to the superior rectus is involved in a meningeal inflammatory process. He showed that the fibres destined for the levator palpebrae superioris form a separate fasciculus partially

enveloping the main nerve trunk, and he suggested that they are thereby more liable to damage. At present there is not sufficient evidence to accept or discard this theory.

THE ISOLATED REFLEX PARALYSIS TO LIGHT

There probably are two distinct pathways for the light- and the near-reflexes, that for the light reflex being more vulnerable to disease processes and to syphilis in particular. But there is insufficient information to decide if separation of the pathways occurs centrally or at the periphery. The novel idea put forward by Apter (1954) that the pupillary near-reflex is a mechanical result of the forward movement of the ciliary muscle during accommodation, is worthy of further enquiry. It is relevant that the reaction of the pupil to convergence in the tabetic patient is not lost with the advent of presbyopia. This does not altogether refute Apter's theory because there is evidence that the ciliary muscle maintains its power of contraction in spite of the progressive hardening of the crystalline lens (Fincham, 1955).

It must be admitted that since Argyll Robertson's clinical description in 1869 of the pupillary changes which bear his name and which were later found to be often caused by syphilis, little or no progress has been made in the elucidation of the mechanism of these abnormal pupils. Pathological investigations have been disappointing, and it is to be hoped that experimental and pharmacological research may prove more rewarding in the future.

THE HOLMES-ADIE SYNDROME

THE MECHANISM OF THE TONIC RESPONSE

The variability of the pupillary abnormalities in the Holmes-Adie syndrome has been stressed by references to the literature and by the clinical data of the twenty patients presented in this thesis.

Differentiation from syphilitic pupils may be difficult because either disorder may cause bilaterally small and irregular pupils, with loss of the reaction to light and preservation of the reaction to convergence. It is true that in the Holmes-Adie syndrome marked miosis and atrophy of the iris are uncommon, but the most reliable sign is undoubtedly the slow constriction of the pupil induced by convergence and the even slower dilatation that follows relaxation of convergence. This sluggishness of movement, together with the less common excessive response to convergence, are the characteristic features of the "tonic pupil".

Because the tonic reaction is so distinctive, the elucidation of its physiopathology assumes some importance. Two main hypotheses have been formulated to account for the tonic reaction: first, a disturbance of sympathetic function; second, an increased sensitivity of the iris muscle following partial parasympathetic denervation. Evidence was presented in this thesis in favour of discarding the first hypothesis: neither a lesion nor an overaction of the sympathetic innervation is present. It was shown, on the other hand, that the pupils vary in their sensitivity to three different parasympathomimetic drugs (acetyl B methyl choline, eserine and pilocarpine). The reaction to pilocarpine was quantified and found to

be increased in pupils showing the tonic reaction. And further, the sensitivity to pilocarpine bore a direct relationship to the range of movement caused by convergence, and to the time taken by the pupil to dilate again.

The reaction to convergence is likely to depend on the degree to which the parasympathetic innervation is functioning. This supposition was supported by finding that when antagonism to the parasympathetic innervation was removed by sympathetic block, the resulting constriction equalled that which could be caused by convergence before the block. Thus, there is evidence that in the tonic pupil, parasympathetic function is partly preserved and the iris muscle is hypersensitive to parasympathomimetic drugs.

These facts substantiate the theory put forward by Soheie (1940) that the tonic reaction is due to surviving parasympathetic fibres releasing acetyl choline which diffuses to neighbouring denervated, and therefore sensitized, muscle fibres. This process is analogous to the Philipeaux-Vulpian phenomenon, in which contraction of the tongue can be obtained by stimulating the chorda tympani some days after section of the hypoglossal nerve. This pseudo-motor effect is thought to result from a diffusion of acetyl choline from the stimulated autonomic nerve endings to the denervated and sensitized striated muscle fibres (Cannon and Rosenblueth, 1949). The contraction is often slow and excessive - in fact, very much like that found in the tonic pupil.

Is there any difference between the action of acetyl choline released at nerve endings and that of different parasympathomimetic drugs applied locally, as in this investigation? There would not

appear to be, for experimental denervation of the iris results in hypersensitivity to all parasympathomimetic substances including acetylcholine, whether these be injected parenterally or instilled in the conjunctiva (Bender and Weinstein, 1940; Keil and Root, 1941 and 1942; Heidle, 1950). The effect of acetyl B methyl choline, eserine and pilocarpine on the pupil can be taken to mirror the action of acetylcholine under natural conditions.

THE SITE OF THE LESION

The development of pupillary paralysis with subsequent hypersensitivity to parasympathomimetic drugs, places the site of the disturbance along the parasympathetic pathway between the third nerve nucleus and the short ciliary nerve endings. It remains uncertain whether the pre- or post-ganglionic nerves are primarily affected, but the evidence favours a post-ganglionic lesion.

In lesions of the sympathetic, sensitivity is usually more marked after post-ganglionic than after pre-ganglionic denervation, but Keil and Root (1942) pointed out that with parasympathetic denervation of the cat's iris the two different sections are often equal in their effect. On the other hand, there are records of tonic pupils developing after injuries or tumours established as affecting the ciliary ganglion or short ciliary nerves (Axenfeld, 1906; Ohm, 1907; Cords, 1930; Garcin and Kipfer, 1936). Moreover, the constant irregularity of the pupil points to a selective segmental denervation, such as would be produced by partial and irregular involvement of the short ciliary nerves. The ciliary ganglion was thought to be the site of the lesion also by Magitot (1911), Scheie

(1940) and Leathart (1942).

CLASSIFICATION OF THE ABNORMAL PUPIL

It has been shown that different pupils vary a great deal in the degree to which they exhibit the tonic reaction. The two extreme types may be termed the "paralytic" and truly "tonic" pupils. The paralytic pupil represents the first stage of the disorder; it fails to constrict to convergence and to a stellate ganglion block, and is relatively insensitive to parasympathomimetic drugs. The tonic pupil, on the other hand, is found at a later stage when there is evidence of recovered parasympathetic function and sensitization has developed. It responds to convergence, sometimes in an exaggerated way, and to interruption of the sympathetic innervation; slow contraction and relaxation are evident, together with an enhanced reaction to parasympathomimetic drugs.

It must be pointed out that the common enlarged pupil is not necessarily a paralytic one. Two of the largest pupils in this series (Cases 2 left and 11) were remarkably tonic in their response, and became exceedingly small after a stellate ganglion block; this indicated that their size was maintained by sympathetic activity. The two types of abnormal pupil may be seen in the same patient - Case 2 had a paralytic pupil on the right and a tonic one on the left.

ACCOMMODATION

It was shown in this thesis that patients who have had an abnormal pupil for several months exhibit a slow contraction of the

corresponding ciliary muscle, which also becomes hypersensitive to pilocarpine. This tonic accommodation is strictly analogous to the tonic reaction of the pupil to convergence, and the hypersensitivity of the ciliary muscle is proportionate to that of the sphincter pupillae. There is good evidence, therefore, for supposing that the abnormal processes affecting the pupil and accommodation are identical. Furthermore, just as the tonic pupil is often preceded by a paralytic one, it is likely that delayed accommodation follows on a paresis of accommodation.

This does not mean that every patient with the Holmes-Adie syndrome has at some time had a paralysis of accommodation. In many cases, no symptoms are ever noticed, though close enquiry will often elicit the history of a forgotten episode of blurred vision. The development of symptoms depends a great deal on the degree to which the patient relies on his accommodative power. This reliance on accommodation is lessened in myopia and absent in presbyopia, so that myopic and middle aged subjects may not become aware of abnormal accommodation. With hypermetropia or astigmatism, however, a sudden paralysis of accommodation may prove to be temporarily disabling, especially if it occurs in the young.

Certainly, abnormal accommodation is a very common complication, and may prove to be even commoner when improved methods of diagnosis become available. The application of perfected means of timing accommodation may enable us to diagnose the more elusive forms of tonic accommodation. It may also prove possible with the "methyl test" to recognise hypersensitivity of the ciliary muscle in the same way as hypersensitivity of the sphincter pupillae.

THE EVOLUTION OF THE HOLMES-ADIE SYNDROME

The course of this disorder is therefore one of paralysis followed by tonicity, affecting both the pupil and accommodation. The two eyes may be involved simultaneously or, as is more common, separately after an interval of months or years. Tendon reflexes may be gradually abolished. The Holmes-Adie syndrome is therefore truly progressive, a fact which has already been emphasized by Holmes (1931) and Stürup (1946).

THE FUTURE

There remain many gaps in our knowledge. Experimental work shows that increased sensitivity of the denervated iris develops within a few hours, whereas a much longer period may elapse before the same phenomenon develops after an internal ophthalmoplegia in the human. In one patient reported in this thesis, the clinical features of the tonic reaction became manifest only about three months after increased sensitivity to pilocarpine had been detected. Though it is easy to see why the completely denervated iris of internal ophthalmoplegia does not show a tonic response (there being no release of acetylcholine), it is far from clear why the pupil does not constrict to locally administered parasympathomimetic substances. This also is in contrast with the response to pilocarpine and eserine of the experimentally denervated iris in animals.

These and other questions will need to be answered in the future. It may be that an atropine-like substance is released at the myoneural function in the early stage of the disorder, and that it interferes with nerve transmission and reaction to parasympathomimetic

drugs. It may prove rewarding to search for such a substance, and to test on the abnormal pupil the effect of new drugs known to act at the myo-neural function.

An alternative explanation is suggested by the work of Murray and Thompson (1957). They showed that recovery of function after partial sympathectomy in cats depends, not on hypersensitivity, but on collateral sprouting of the surviving sympathetic fibres. By the end of four to eight weeks, the sprouts form new synapses with the denervated ganglion or effector cells. This phenomenon has not been demonstrated yet in the parasympathetic system, but if it were, it would account more readily for the delay in recovery of the pupil, noted in this study. The tonic pupil would therefore result from two combined sequels to a parasympathetic lesion - hypersensitivity of the effector cells and formation of new connections by sprouting.

CHAPTER VIII

SUMMARY

1. This thesis is a study of the nervous control of the pupil and of accommodation in health, syphilis and the Holmes-Adie syndrome.
2. A review of the literature revealed that the following questions remain unsolved:-
 - (i) Is there a sympathetic regulation of accommodation?
 - (ii) Are there separate pathways for the light- and near-reflexes? If there are, where is the light-reflex pathway damaged in syphilis?
 - (iii) What is the cause of miosis in the syphilitic pupil?
 - (iv) What is the nature of the tonic reaction of the pupil and of accommodation in the Holmes-Adie syndrome?
3. This thesis deals with questions (i), (iii) and (iv). Answers were found to questions (i) and (iv). Only a negative contribution was made to problem (iii).
4. The chief methods of investigation were procaine sympathetic blocks and sympathetic stimulation by cocaine eye-drops; the para-sympathetic innervation was studied with parasympathomimetic drugs and homatropine locally instilled. Precise pupillography was devised for timing the tonic reaction. Accommodation was accurately measured with Fincham's coincidence optometer.
5. The following patients and subjects were examined:-
 - (i) 5 patients with Horner's syndrome of central nervous causation.
 - (ii) 10 patients with syphilitic pupils.

(iii) 20 patients with the Holmes-Adie syndrome.

(iv) 35 subjects with normal eyes.

6. Results

a. In the Normal Eye. --

(i) If the parasympathetic innervation is temporarily paralysed with homatropine, a superadded sympathetic block fails to constrict the dilated pupil.

(ii) Locally instilled cocaine fails to dilate the pupil when its sympathetic control is completely lost.

(iii) Neither stimulation nor blocking of the sympathetic innervation alters normal accommodation.

b. In the Syphilitic Pupil. --

A sympathetic block does not convert a large syphilitic pupil into a mictic one.

c. In the Holmes-Adie Syndrome. --

(i) The Holmes-Adie pupil does not differ fundamentally from the normal pupil in its response to sympathetic stimulation or block. A sympathetic block does not alter the tonic reaction of the pupil.

(ii) Increased sensitivity of the tonic pupil to different parasympathomimetic drugs is often found. The sensitivity to pilocarpine varies directly with the tonic reaction.

(iii) In long-standing cases, accommodation is not reduced in range, but is delayed. There is an hypersensitivity of the ciliary muscle, which is proportionate to that

of the sphincter pupillae.

7. Conclusions

a. In the Normal Eye. -

- (i) A sympathetic lesion cannot prevent dilatation of the pupil by homatropine.
- (ii) Cocaine eye-drops may be used as a test of remaining sympathetic innervation of the iris.
- (iii) There is no sympathetic control of normal accommodation.

b. In the Syphilitic Pupil. -

A sympathetic lesion cannot cause the miosis.

c. In the Holmes-Adie syndrome. -

- (i) Sympathetic activity is neither deficient nor excessive.
- (ii) Hypersensitivity of the sphincter pupillae to acetylcholine is important in the causation of the tonic pupil.
- (iii) Accommodation and the pupil both show a comparable tonic reaction. The pathological processes affecting the pupil and accommodation are probably identical.
- (iv) There are two main types of abnormal pupil - paralytic and tonic; the stage of paralysis is usually followed by a stage of tonicity, both of the pupil and of accommodation. The course of the disorder is progressive.

8. Tentative suggestions were made for the investigation of outstanding problems.

A P P E N D I X

CASE REPORTS

Case 1

A young single woman suddenly sensed a blurring of the vision of the left eye, and on looking in a mirror she noticed that the left pupil was somewhat larger than the right. Next morning she found that the left pupil had enlarged even further, and thereafter it remained fully dilated. Examination two months later revealed a large pupil, fixed to light and convergence, with paralysis of accommodation in the same eye and a reduction of visual acuity to J.7. Eleven months after the onset of symptoms she was again able to read J.1, but accommodation from distant to close vision required 13 seconds. The pupil still failed to respond to both light and convergence, and the tendon reflexes remained normal. In view of the development of delayed accommodation this case of ophthalmoplegia interna was included in the series.

Case 2

This young girl had suffered from an intermittent divergent heterotropia since the age of 5, but had compensated for it fairly well until now. During the course of her clerical work she suddenly noticed a dimness in the vision of the left eye, and her attention was drawn to an enlargement of the pupil on that side. Thereafter, the tendency to divergence of the eyes became accentuated and she had to close the left eye while at work to avoid troublesome diplopia. Examination showed a left tonic pupil and absent knee and

ankle jerks. Sixteen months later (October 2, 1955), while she was reading, the right eye became blurred, and to continue reading she had to close that eye and revert to fixation with the left eye. She was examined within two days of this relapse, and it was found that the right pupil was enlarged and reacted poorly to light and accommodation. Visual acuity on that side remained at J.1, but 15 seconds were required for accommodation from a distance, and the near point was 25 cm. All tendon reflexes were absent except the right biceps jerk. Frequent examinations over the next few days revealed progressive paralysis of accommodation. On October 6 she could only read J.3 with the right eye, and on October 15 vision was restricted to J.8 and the near point increased to 58 cm., while distant vision remained relatively unaltered. At the same time the pupil became further enlarged, fixed to light, and only slightly responsive to accommodation. Her heterophoria was now decompensated and she developed an intermittent divergent squint for close vision and a convergence insufficiency. With a plus 3 lens in front of the right eye she could see J.1, but the left eye became divergent, whereas without glasses she depended on the left eye and the right eye deviated outwards.

Case 15

A man of 34 had attended an ophthalmic department in September, 1954, complaining of a sensation of glare in the left eye which had developed suddenly. At this time the left pupil was found to be dilated and fixed to light and convergence. When seen 16 months later, his symptoms had subsided and the pupil was irregular and typically tonic, taking 20 seconds to dilate after relaxation of

convergence. During a medical examination in 1939 it had been noted that the tendon reflexes in the legs were sluggish or absent.

Case 20

A 51-year-old dock worker was admitted to hospital with pneumonia, where it was noted that he had a left-sided ptosis and an oval enlarged pupil which reacted only slightly and sluggishly to light and convergence. He maintained that the ptosis had been present all his life and that his father, now dead, had also had a drooping upper eyelid. Sweat tests showed anhidrosis on the left side of the face, and the ptosis was therefore ascribed to a lesion of unknown causation in the sympathetic pathway proximal to the bifurcation of the common carotid artery. Clearly, this could not alone account for an irregular, enlarged, and poorly reacting pupil. The following evidence was obtained for including the patient in the series of tonic pupils: pupillary dilatation to $6\frac{1}{2}$ mm. resulted when he was kept in total darkness for 40 minutes, and after exposure to bright daylight the pupil took three minutes to return to a diameter of $3\frac{1}{2}$ mm. This was, therefore, a rare example of the natural occurrence of a tonic pupil with a sympathetic lesion.

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NOTE. - Important references are underlined in red.